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The Western Journal of Medicine

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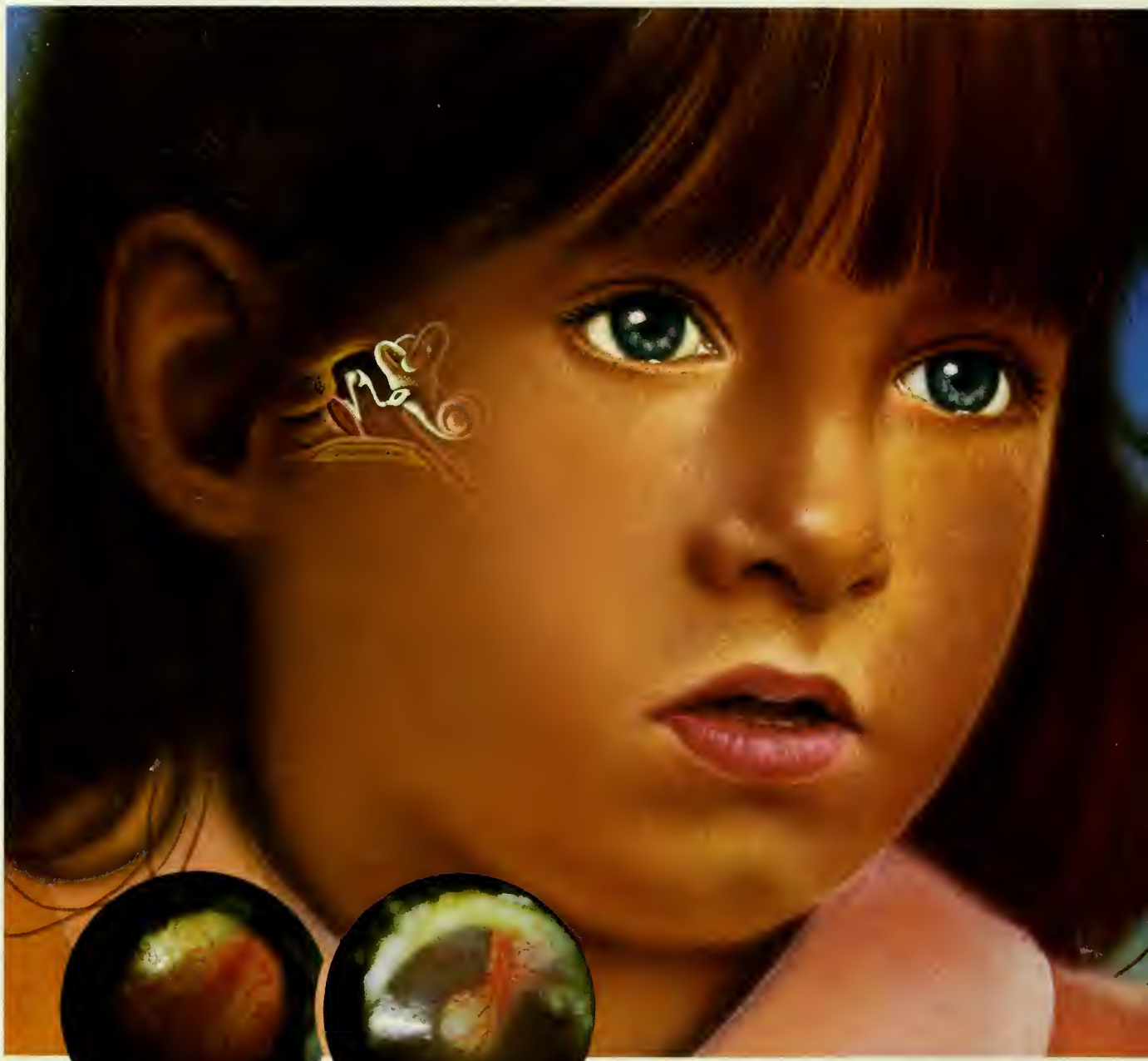

before Otoscopic view of tympanic membrane in a patient who did not respond to ampicillin

after Same patient after ten days of Bactrim (trimethoprim and sulfamethoxazole/Roche) therapy

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References: 1. Klimek JJ *et al: J Pediatr 96:*1087-1089, Jun 1980. **2.** Schwartz RH *et al: Rev Infect Dis 4:*514-516, Mar-Apr 1982. **3.** Cooper J, Inman JS, Dawson AF: *Practitioner 217:*804-809, Nov 1976. **4.** Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. **5.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **6.** Wormser GP, Keusch GT, Heel RC: *Drugs 24:*459-518, Dec 1982. **7.** *Med Lett Drugs Ther 23:*93-95, Oct 30, 1981.

Please see summary of product information on the following page.

References: 1. Klimek JJ *et al: J Pediatr* 96:1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Dis* 4:514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. 7. *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981.

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Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

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Dosage: Not recommended for infants less than two months of age.

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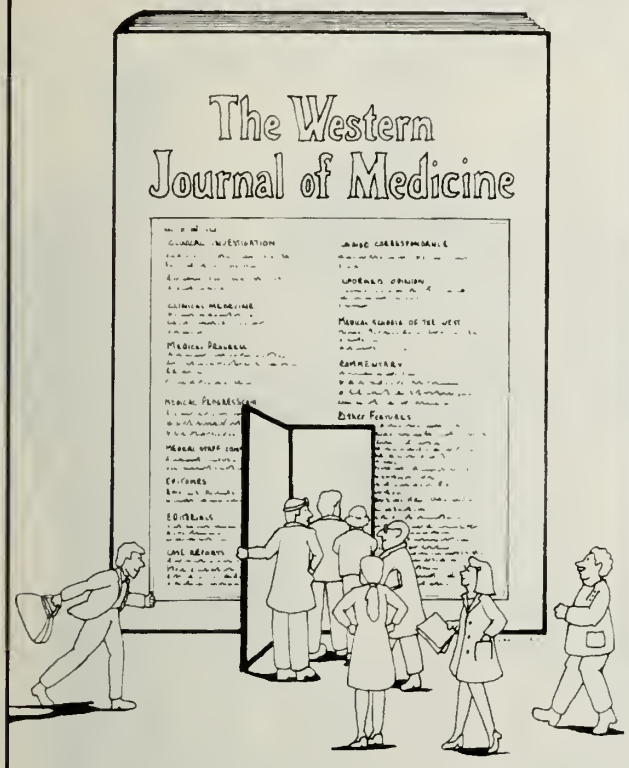

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The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg, and for controlled release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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See previous page for brief summary of prescribing information.

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CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure – Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal – Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of β_2 receptors.

Major Surgery – Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia – Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis – Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: impaired Renal Function – Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients – Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug interactions – Concurrent administration may result in interactions with: Anesthetics, general – exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin) – hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine) – additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, impairment of Fertility – In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy – In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers – Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use – Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular – Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** – Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** – Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** – Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** – Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia. The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System** – reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** – mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic** – agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** – fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** – pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia – Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure – Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension – Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm – Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527D)

References: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Min Electrolyte Metab 8:237-254, 1982. 2. Danesh BJZ, et al: Comparison between short-term renal haemodynamic effects of propranolol and nadolol in essential hypertension: a cross-over study. Clin Sci 67:243-248, 1984. 3. Hollenberg NK: Introduction: β-adrenergic blocking agents–the treatment of hypertension and the kidney. Royal Soc of Med Int Congress and Symposium Series 51:1-8, 1982. 4. Frohlich ED, et al: Long-term renal hemodynamic effects of nadolol in patients with essential hypertension. Am Heart J 108:1141-1143, 1984. 5. Alexander JC, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

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From the Departments of Medicine and Radiology and the Division of Otolaryngology, Department of Surgery, Harbor/UCLA Medical Center, Torrance, California.

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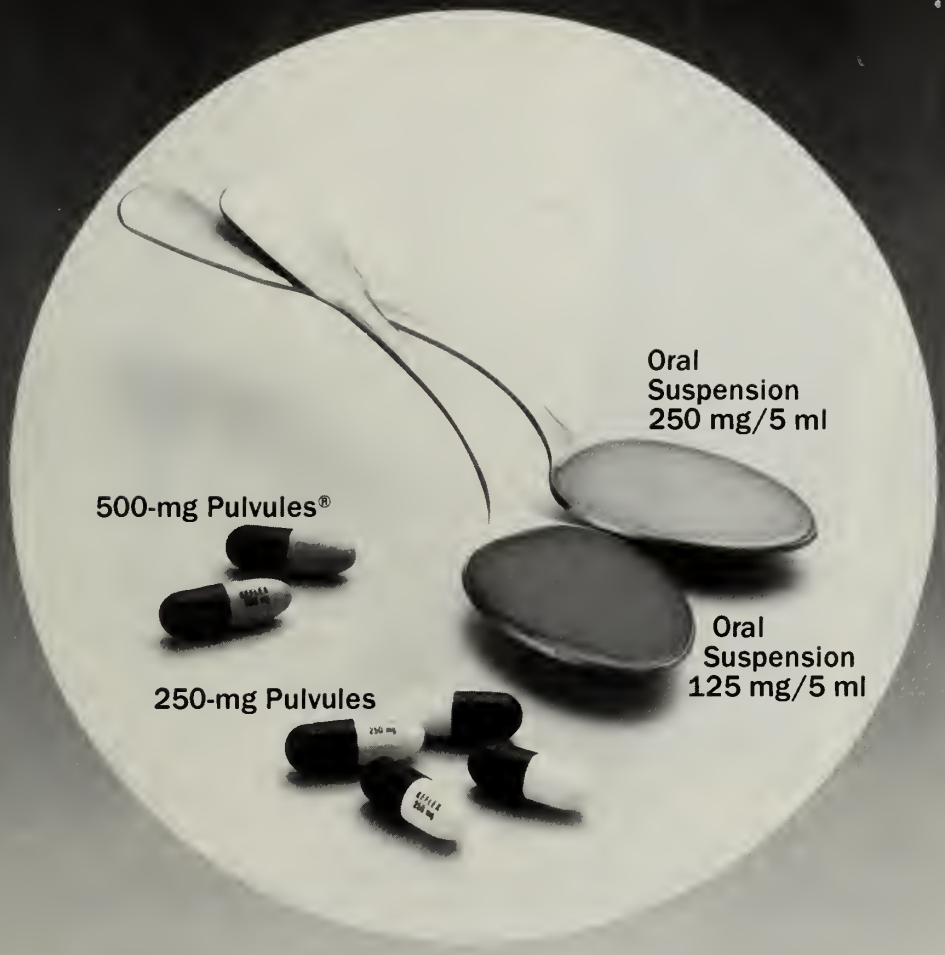

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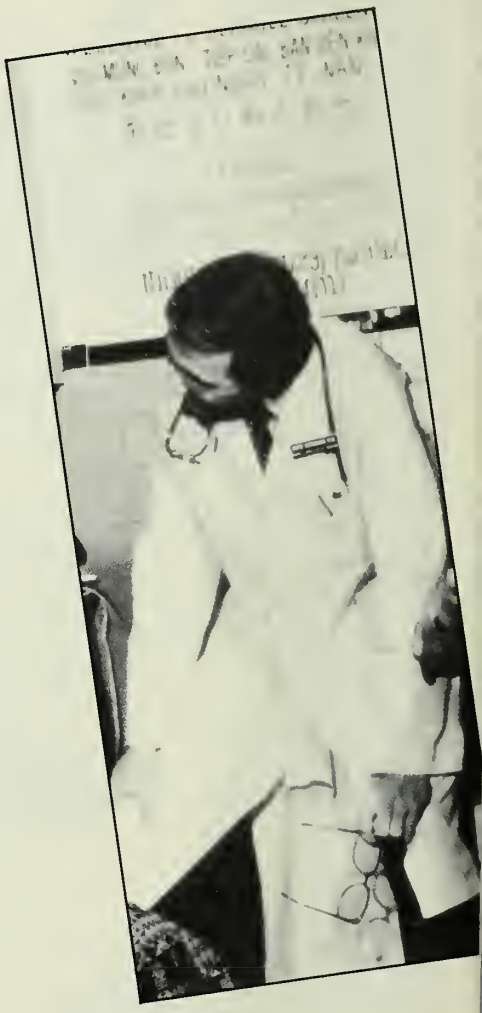

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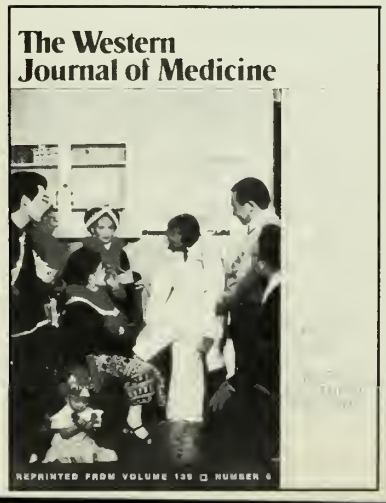

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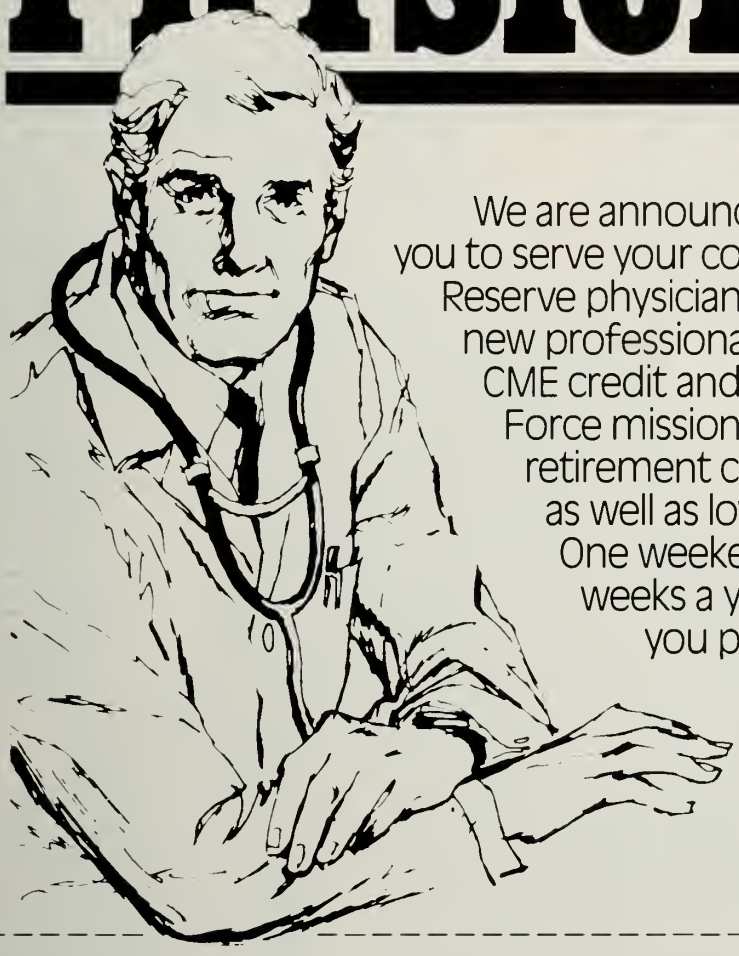

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*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

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Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia, some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

Wyeth Laboratories
Philadelphia, PA 19101

™

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ARTHRITIS ALTERNATIVES—Irma and Laurence Gadd. Facts on File, Inc, 460 Park Ave South, New York, NY 10016, 1985. 161 pages, $14.95.

AN ATLAS OF CRITICAL CARE CHEST ROENTGENOGRAPHY—Lyle D. Victor, MD, Director, Pulmonary Disease Section, Oakwood Hospital, Dearborn, Mich; Radiography Editor: Allen J. Stone, MD, Staff Radiologist, and Photography Editor: Michael P. Sarnacki, MD, Director, Audio Visual Services, Oakwood Hospital. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1985. 284 pages, with 349 illustrations, $45.

ATLAS OF GYNAECOLOGICAL DIAGNOSIS—Abdel Fattah Youssef, Professor and Ex-Chair, Department of Obstetrics and Gynaecology, Cairo University; Senior Gynaecological Surgeon, Kasr El Aini Hospital, Cairo, Egypt. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 179 pages, with illus in color, $32.

BACTERIAL MENINGITIS—Volume 3 of CONTEMPORARY ISSUES IN INFECTIOUS DISEASES—Edited by Merle A. Sande, MD, Professor and Vice Chair, Department of Medicine, University of California, San Francisco, and Chief, Medical Service, San Francisco General Hospital; Arnold L. Smith, MD, Professor of Pediatrics, University of Washington, and Head, Division of Infectious Diseases, Children's Orthopedic Hospital and Medical Center, Seattle, and Richard K. Root, MD, Professor and Vice Chair, Department of Medicine, University of Washington, and Chief, Medical Service, VA Medical Center, Seattle. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 272 pages, $40.

BASIC CONCEPTS IN TERATOLOGY—T. V. N. Persaud, MD, PhD, DSc, Faculties of Medicine and Dentistry, and A. E. Chudley, MD, FRCP(C), Faculty of Medicine, University of Manitoba, Winnipeg, Canada, and R. G. Shalko, MSc, PhD, College of Medicine, East Tennessee State University, Johnson City. Alan R. Liss, Inc, 41 E 11th Street, New York, NY 10003, 1985. 181 pages, $38.

CLINICAL PHARMACOLOGY AND DRUG TREATMENT IN THE ELDERLY—Edited by Kevin O'Malley, MD, PhD, FRCPI, FRCP(Edin), Professor, Department of Clinical Pharmacology, Royal College of Surgeons in Ireland and The Blood Pressure Clinic, The Charitable Infirmary, Dublin. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 217 pages, $35.

THE HEREDITARY ATAXIAS AND RELATED DISORDERS—Volume 6 in CLINICAL NEUROLOGY AND NEUROSURGERY MONOGRAPHS—A. E. Harding, MD, MRCP, Lecturer in Neurology, Institute of Neurology and Royal Postgraduate Medical School, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 260 pages, $56.

HYPOTENSIVE ANAESTHESIA—Edited by G. E. H. Enderby, FFARCS, honorary Consultant Anaesthetist, Queen Victoria Hospital, East Grinstead, Sussex, UK. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 281 pages, $30.

INTERPRETATION OF CLINICAL LABORATORY TESTS—REFERENCE VALUES AND THEIR BIOLOGICAL VARIATION—Edited by Gérard Siest, PhD, Head, Laboratory Department, Center for Preventive Medicine, Vandoeuvre-les-Nancy, and Professor of Biochemical Pharmacology, University of Nancy; Joseph Henny, PhD, and Françoise Schiele, PhD, Directors, Laboratory Department, Center for Preventive Medicine, Vandoeuvre-les-Nancy, France, and Donald S. Young, MB, PhD, Department of Laboratory Medicine, Mayo Clinic and Foundation, Rochester, Minnesota. Biomedical Publications, PO Box 8209, Foster City, CA 94404, 1985. 455 pages, $42.50.

LIFETIME CARE OF THE PARAPLEGIC PATIENT—Edited by Sir George M. Bedbrook, Kt, OBE, OStJ, MS(Melb), HonMD(WA), HonFRCS(Ed), FRCS FRACS DPRM(Syd), Senior Spinal Surgeon, Royal Perth Hospital and Royal Perth Rehabilitation Hospital, Perth, Western Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 263 pages, $55.

McALPINE'S MULTIPLE SCLEROSIS—W. B. Matthews, DM, FRCP, Professor of Clinical Neurology, University of Oxford; E. D. Acheson, MA, BCh, DM, FRCP, Chief Medical Officer, Department of Health and Social Security, Alexander Fleming House, London; J. R. Batchelor, MD, Professor of Immunology, Hammersmith Hospital, London, and R. O. Weller, BSci, MD, PhD, FRCPath, Professor of Neuropathology, University of Southampton, Southampton, UK. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 358 pages, $59.

MAGNETIC RESONANCE IMAGING OF THE BRAIN, HEAD, AND NECK: A TEXT—ATLAS—William G. Bradley, Jr, MD, PhD, Director, NMR Imaging Laboratory, Huntington Medical Research Institutes and Department of Radiology, Huntington Memorial Hospital, Pasadena, California, and Assistant Clinical Professor of Radiology, University of California, San Francisco; W. Ross Adey, MB, BS, MD, Associate Chief of Staff for Research and Development, Pettis Memorial Veterans' Hospital, and Professor of Physiology and Surgery, Loma Linda University School of Medicine, and Anton N. Hasso, MD, Director, Neuroradiological Section, Loma Linda University Medical Center, and Professor of Radiology, Loma Linda University School of Medicine, Loma Linda, California. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1985. 125 pages, $65.

MANAGING INCONTINENCE—Edited by Cheryle Gartley, Founder and President of the Simon Foundation, Wilmette, Illinois. Jameson Books, 722 Columbus St, Ottawa, IL 61350, 1985. 150 pages, $12.95.

MEDICAL MALPRACTICE—A PREVENTIVE APPROACH—William O. Robertson, MD, Professor, Department of Pediatrics, University of Washington; Head, Washington State Medical Association Risk Management Program, and Director of the Quality Assurance Program, Children's Orthopedic Hospital, Seattle. University of Washington Press, Seattle, WA 98105, 1985. 222 pages, $20.

MEDICAL SCIENCE AND THE ADVANCEMENT OF WORLD HEALTH—Edited by Robert Lanza, MD. Praeger, 521 Fifth Ave, New York, NY 10175, 1985. 271 pages, $39.95.

MEDICINE IN THE TROPICS—Second Edition—Edited by A. W. Woodruff, CMG, MD, PhD, FRCP, FRCPE, CTM&H, Professor of Medicine, University of Juba, Sudan, and Consulting Physician, Hospital for Tropical Diseases, London, and S. G. Wright, MB, MRCP(UK), Senior Lecturer, Department of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, and Honorary Consultant Physician, Hospital for Tropical Diseases, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 636 pages, $62 (paperback).

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

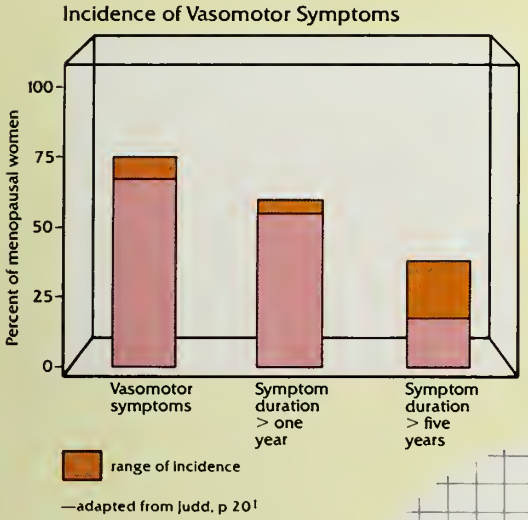
Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

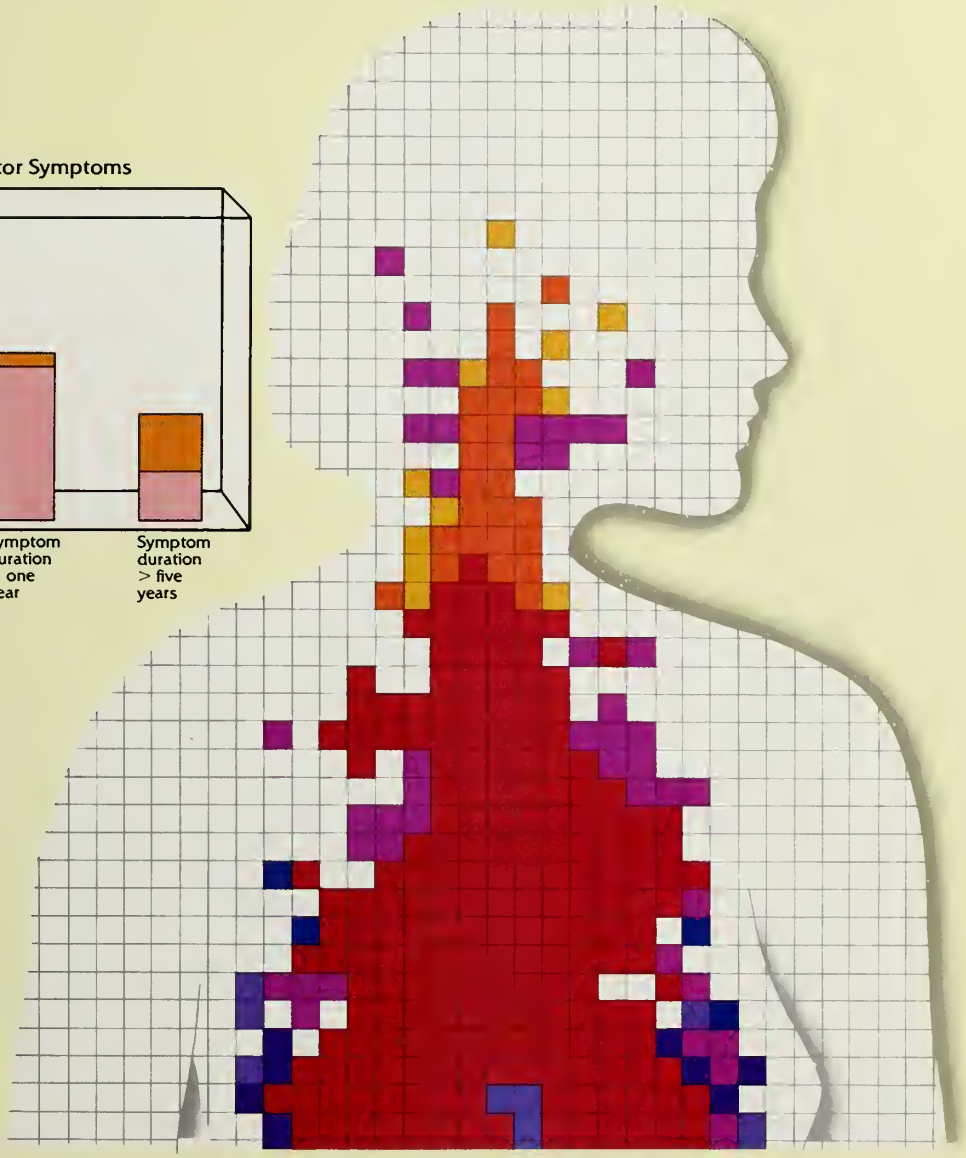
All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION





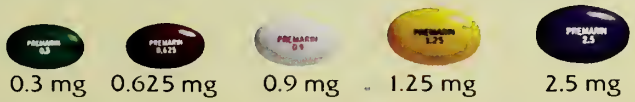
PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years! These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[2]—the treatment of choice for moderate to severe vasomotor symptoms.[3] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

PREMARIN®

(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

Please see last page for brief summary of full prescribing information.

VAGINAL ATROPHY THAT INTERFERES WITH SEXUALITY

PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

PREMARIN®

(CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream

0.625 mg/g

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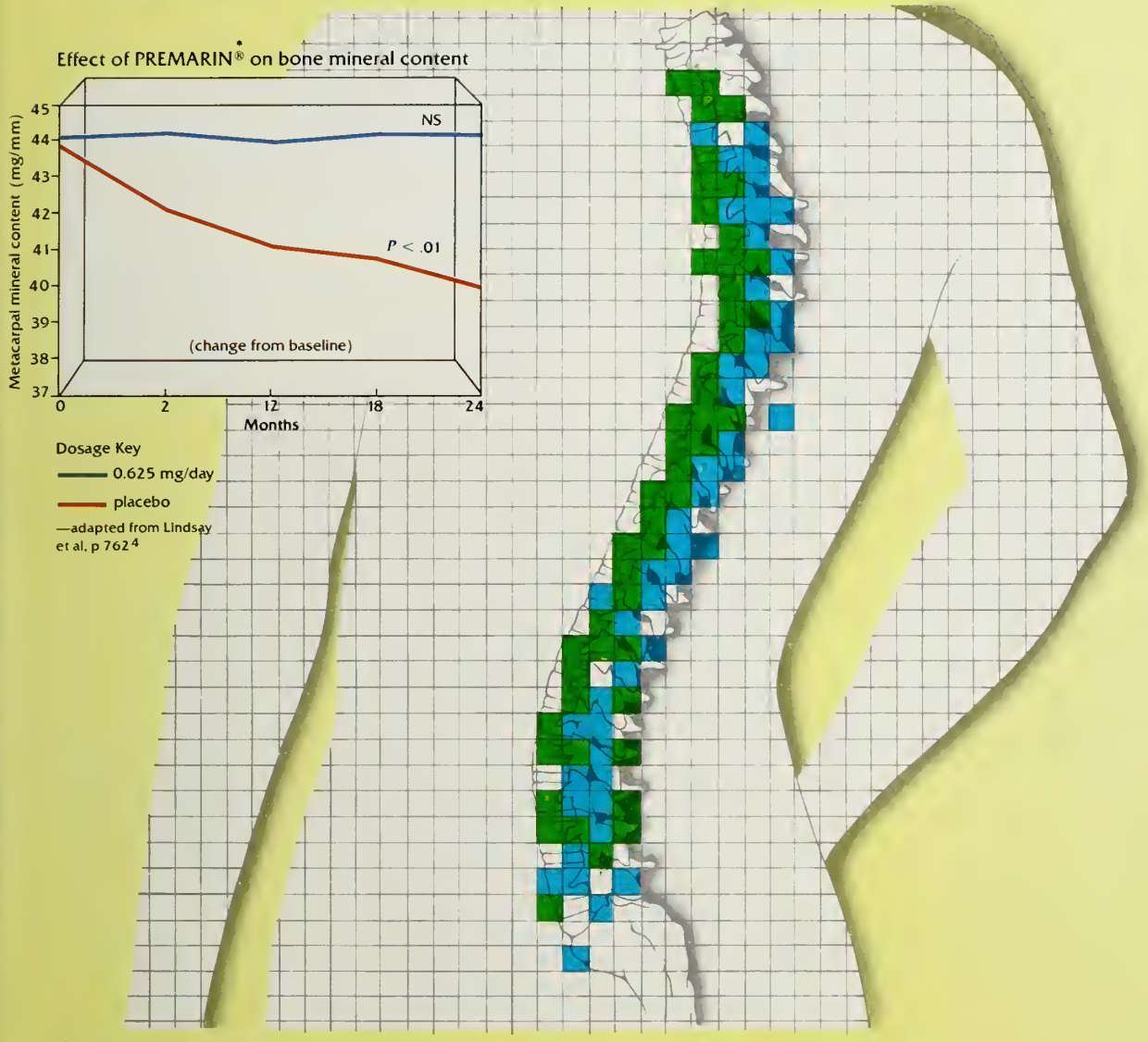
Please see last page for brief summary of full prescribing information.

POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES



PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.[5] The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.[6]

To minimize osteoporotic damage, the condition must be detected early and treated promptly. For many patients, PREMARIN is optimal therapy for osteoporosis, as part of a comprehensive program that includes exercise, good nutrition, and calcium supplements. In a controlled study of postmenopausal and oophorectomized women, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) doses of 0.625 mg/day prevented loss of metacarpal mineral content (see graph above).[4]

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE. May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **4340R2/785**

REFERENCES: 1. Judd HL: After the menopause. *Transition* 1983;1:19-30. 2. Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 3. Meldrum DR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983;1(February):11-17. 4. Lindsay R, Hart DM, Clark DM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984;63:759-763. 5. Katz WA: *Rheumatic Diseases: Diagnosis and Management*. Philadelphia, JB Lippincott Co, 1977, p 672. 6. Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983;22(November):116-131.

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★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.**

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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

August 16-18—**Summer Conference on Allergy, Rheumatology and Orthopedic Surgery.** Scripps Clinic & Research Foundation at Sherwood Hall, La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. 14 hrs. Fee: $25-$195. Contact: Bonny A. Mower, Scripps Clinic & Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

ANESTHESIOLOGY

August 8-11—**Clinical Neuroanesthesia Conference.** UCSD at Hotel Intercontinental, San Diego. Thursday-Sunday. 22 hrs.

September 7-11—**Case Conference on Clinical Anesthesia.** California Society of Anesthesiologists and Travenol Laboratories at High Sierra Hotel, Lake Tahoe, NV. Saturday-Wednesday. 10 hrs. Contact: Linda P. Londerville, CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo, CA 94401. (415) 348-1407.

September 27-29—**Anesthesia Practice, 1985.** Anesthesiology Educational Foundation at Monterey. Friday-Sunday. 10.5 hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles, CA 90024.

CARDIOLOGY

July 19-21—**Cardiovascular Fitness Sports Medicine and Nutrition.** Mercy Medical Center, Redding. Friday-Sunday. Fee: $100. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding 96099. (916) 243-2121.

July 19-21—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Marriott Hotel, Newport Beach, CA. Friday-Sunday. 13 hours. Fee: $295. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

July 29-August 3—**Doppler and 2-D Echocardiography.** The Institute for Medical Studies at Anaheim. Monday-Saturday. 33 hrs. Contact: Kim Stroich, IMS, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 494-4499.

August 1—**Vascular Surgery.** UCD at Sacramento. Thursday.

August 2-4—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado at Disneyland Hotel, Anaheim. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

August 3—**Non-Invasive Vascular Diagnostic Techniques: Conventional & New Imaging Modalities.** UCD at UC Medical Center, Sacramento. Saturday. 7 hrs.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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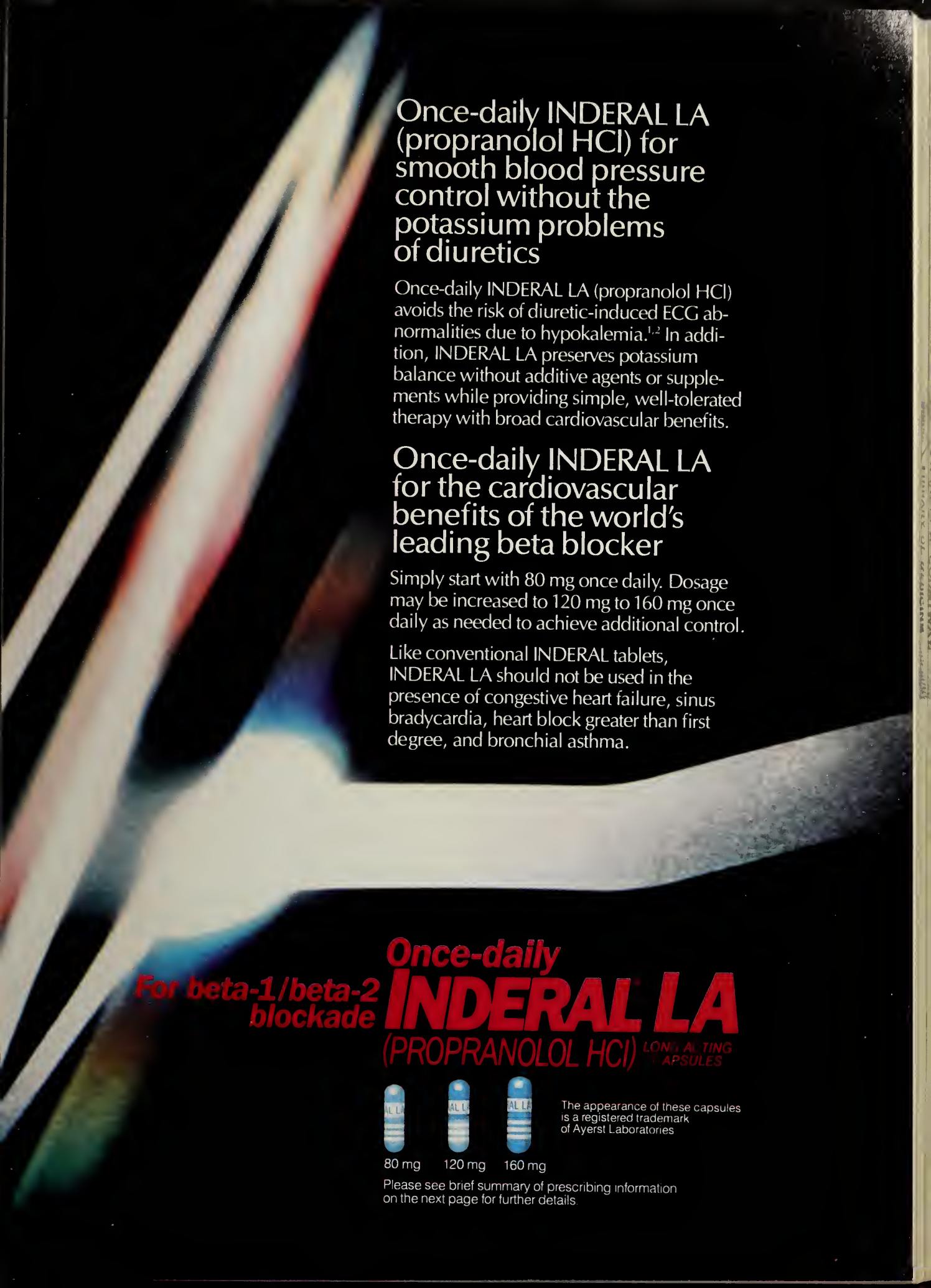
Right from the start in hypertension...



Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[1,2] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

INDERAL LA

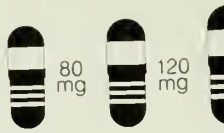
(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories

Please see brief summary of prescribing information on the next page for further details.

Once-daily
For beta-1/beta-2 blockade INDERAL® LA
(PROPRANOLOL HCl) LONG ACTING CAPSULES



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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg and 160 mg capsules

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

REFERENCES

1. Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768. **2.** Holme I, Helgeland A, Hjermann I, et al. Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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(Continued from Page 23)

August 11-16—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sunday-Friday.

August 16-18—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. Fee: $190-295. Contact: Medical Education Resources, 5808 So. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

September 19-21—**Echocardiography Technologist Certification Review.** The Institute for Medical Studies at Los Angeles. Thursday-Saturday. Contact: Kim Stroich, IMS, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 495-4499.

September 21—**Pulmonary Medicine.** UCSF at Fresno. Saturday.

September 26-28—**Cardiology Update, 1985.** American College of Cardiology at Quail Lodge, Carmel. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

September 30-October 4—**Comprehensive Review in Vascular Surgery** UCLA at Miramar Sheraton, Santa Monica. Monday-Friday. 32 hrs.

EMERGENCY MEDICINE

August 12-16—**Wilderness Medicine.** UCSD at Lake Tahoe, NV. Monday-Friday. 23 hrs.

August 26-30—**Topics in Emergency Medicine.** UCSF at Holiday Inn on Union Square, San Francisco. Monday-Friday. 33 hrs.

September 14-21—**Topics in Emergency Medicine.** International Conferences at Hawaii. Saturday-Saturday. 10 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

September 24-26—**Postgraduate Institute for Emergency Physicians: Advanced Procedures Laboratory.** UCSD at San Diego. Tuesday-Thursday. 3 hrs. Fee: $250.

INTERNAL MEDICINE

August 18-23—**New Advances in Internal Medicine: Clinical Applications.** UCD at Napa Valley. Sunday-Friday.

August 31-September 3—**Advances in Internal Medicine Postgraduate Course 1985.** UCSD at Sheraton Harbor Island East, San Diego. Saturday-Tuesday. 25 hrs.

September 12-14—**Internal Medicine at the Monterey Jazz Festival.** UCI at Monterey. Thursday-Saturday. 12 hrs. Contact: Kim Stroich, Institute for Medical Studies, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 495-4499.

September 20-21—**Internal Medicine Symposium.** Southern California Permanente Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. Contact: Judy Harrison, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

September 30-October 2—**Frontiers in Clinical Nephrology—1985.** UCLA at Mission Inn, Sonoma. Monday-Wednesday. 22 hrs. Fee: $395.

OB/GYN

September 28—**Clinical Ultrasound—Update and Ob/Gyn.** Sacramento Radiology Research and Education Foundation at Sacramento. Saturday. 6 hrs. Fee: $50-$75. Contact: SRREF, PO Box 19184, Sacramento, CA 95819.

OPHTHALMOLOGY

September 29-October 4—**American Academy of Ophthalmology Annual Meeting** at San Francisco. Sunday-Friday. Contact: AAO, PO Box 7424, San Francisco, CA 94120. (415) 921-4700.

PSYCHIATRY

July 16-August 27—**The Psychology of Aging.** UCLA Extension at Los Angeles. Tuesdays. Fee: $115. Contact: UCLA Extension, PO Box 24901, Los Angeles, CA 90024. (213) 825-2301.

September 13-15—**Guided Imagery (Advanced).** Institute for the Advancement of Human Behavior at San Francisco. Friday-Sunday. 18 hrs. Fee: $245-$350. Contact: IAHB, 4370 Alpine Rd., Ste. 205, Portola Valley, CA 94025. (415) 851-8411.

RADIOLOGY

August 7-10—**The Assessment of Extracranial Arterial Disease by Duplex Scanning.** The Institute for Medical Studies at Newport Beach. Wednesday-Saturday. 18 hrs. Contact: Kim Stroich, IMS, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 495-4499.

August 27-30—**Radiology Conference.** Northern California Radiology Society at Napa Valley. Tuesday-Friday. 20 hrs. Fee: $275-$345. Contact: Sacramento Radiology Research & Education Foundation, PO Box 18184, Sacramento, CA 95819.

September 1-5—**2nd Annual Radiology and Biology of Physics.** UCSD at Town and Country Hotel, San Diego. Sunday-Thursday. 28 hrs. Fee: $375. Con-

(Continued on Page 30)

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ibuprofen

a stronger reason to prescribe Motrin Tablets

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Extra-Strength Motrin Tablets— a convenient way to tap the full potential of Motrin:

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expands the dosage convenience of MOTRIN Tablets—makes it even easier to adjust the dosage of MOTRIN to each patient's needs...the new dosage range of up to 3200 mg/day can be achieved on a q.i.d. regimen. Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is about half that seen with aspirin.

provides economy...patients should pay less for MOTRIN Tablets than comparable dosages of Clinoril, Feldene, or Naprosyn.

provides, above all, the experience-proven efficacy and safety profile of *Motrin.* MOTRIN continues to be America's most often prescribed nonsteroidal anti-inflammatory agent.

Please turn the page for a brief summary of prescribing information.

Upjohn

The Upjohn Company, Kalamazoo, Michigan 49001

Motrin® Tablets
(ibuprofen)
Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis. Relief of mild to moderate pain and primary dysmenorrhea. Safety and efficacy in children are not established
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with MOTRIN.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.
MOTRIN can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, blurred vision, skin rash, weight gain, or edema. Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when MOTRIN is added.
The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (eg, eosinophilia, rash, etc.), MOTRIN should be discontinued.
In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.
Drug interactions—*Aspirin:* used concomitantly may decrease MOTRIN blood levels.
Coumarin: bleeding has been reported in patients taking MOTRIN and coumarin.
Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal, of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.
Incidence Greater Than 1% (but less than 3%)—Probable Causal Relationship
Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).
Incidence Less Than 1%—Probable Causal Relationship**
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence Less Than 1%—Causal Relationship Unknown**
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis, cataracts; **Hematologic:** Bleeding episodes (eg, epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction, acidosis; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **Renal:** Renal papillary necrosis.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Do not exceed 3200 mg/day.
Rheumatoid arthritis and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
How Supplied:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
Bottles of 500	Bottles of 500	Bottles of 100
Unit-dose package of 100	Unit-dose package of 100	Bottles of 500
Unit of Use bottles of 100	Unit of Use bottles of 100	

Caution: Federal law prohibits dispensing without prescription. *For additional product information, see your Upjohn representative or consult the package insert.*
*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
Upjohn The Upjohn Company Kalamazoo, Michigan 49001 USA
MED B-8-S
June 1985
J-5503

CONTINUING MEDICAL EDUCATION

(Continued from Page 27)

tact: Ryals and Associates, PO Box 610203, DFW Airport, TX 75261. (214) 659-9590.

September 3-6—**The Physics and Biology of Radiology: A Review Course for Diagnostic and Therapy Residents.** UCSD at Town and Country Hotel, San Diego. Tuesday-Friday. 24 hrs. Contact: Ryals and Associates, PO Box 610203, DFW Airport, TX 75261. (214) 659-9590.

September 5-8—**Physics of Diagnostic Radiology.** UCD at Davis. Thursday-Sunday. 25 hrs.

September 7—**12th Annual Radiology Symposium: Endourology/Abscess Localization and Ectopic Pregnancy.** Southern California Permanente at Airport Hilton, Los Angeles. Saturday. Contact: Lilia M. Guerrero, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

SPORTS MEDICINE

July 28-August 1—**Marine and Aquatic Sports Medicine.** UCD at Monterey. Sunday-Thursday.

SURGERY

August 16-18—**Summer Conference on Allergy, Rheumatology and Orthopedic Surgery.** Scripps Clinic and Research Foundation at La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. 14 hrs. Fee: $25-$195. Contact: Bonny A. Mower, Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

September 4-7—**Superficial Anatomy and Cutaneous Surgery for Dermatologists.** UCSD at San Diego. Wednesday-Saturday. 22.5 hrs.

September 18-21—**A Cementless 'Revolution' in Joint Replacement, 1985.** UCLA Extension at Los Angeles. Wednesday-Saturday. 27 hrs. Fee: $100-$475. Contact: UCLA Extension, PO Box 24901, Los Angeles, CA 90024. (213) 825-7186.

OF INTEREST TO ALL PHYSICIANS

August 6-8—**Dermatopharmacology Symposium.** Stanford at Stanford. Tuesday-Thursday.

August 10-11—**Life Review Through the Journal Process.** UCLA Extension at Los Angeles. Saturday-Sunday. Fee: $85. Contact: UCLA Extension, PO Box 24901, Los Angeles, CA 90024. (213) 825-2301.

August 17-18—**Clinical Hypnotherapy for Professionals.** UCLA Extension at Los Angeles. Saturday-Sunday. Fee: $95. Contact: UCLA Extension, PO Box 24901, Los Angeles, CA 90024. (213) 825-2301.

August 17-23—**Fine Needle Aspiration.** UCSF at Marriott Biltmore, Santa Barbara. Saturday-Friday. Fee: $525.

August 21-25—**26th Annual Advanced Seminars in Dermatology.** UCSD at Sheraton Harbor Island West, San Diego. Wednesday-Sunday. 16 hrs.

September 9-13—**Primary Care.** UCSF at Sir Francis Drake, San Francisco. Monday-Friday.

September 11-12—**Perspective on Clinical Nutritution (1985 Postgraduate Course).** American Society for Parenteral and Enteral Nutrition at Cathedral Hill Hotel, San Francisco. Wednesday-Thursday. Contact: ASPEN, 8605 Cameron St., Ste. 500, Silver Spring, MD 20910. (301) 587-6315.

September 12-13—**Monoclonal Antibodies: Diagnostic & Therapeutic Uses in Tumors and Transplantation.** UCD at Hyatt Union Square, San Francisco. Thursday-Friday.

September 12-14—**Kids Have Bones, Too.** UCD at Beverly Garland, Sacramento. Thursday-Saturday.

September 18-19—**53rd Annual Fall Symposium.** American Heart Association at Wilshire Blvd. Hilton, Los Angeles. Wednesday-Thursday. 13 hrs. Fee: $100-$185. Contact: Marianne Joyce, AHA, Greater Los Angeles Affiliate. (213) 385-4231.

September 18-20—**Adolescent and Family Treatment: An Investment for the Future.** The McDonald Center for Alcoholism and Drug Addiction Treatment Center of Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Wednesday-Friday. Fee: $190. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 454-6222.

September 19-22—**International Sex Research Conference/1985 Annual Conference.** The Society for the Scientific Study of Sex, Inc. at Holiday Inn Embarcadero, San Diego. Thursday-Sunday. 14 hrs. Contact: Dwight Dixon, PhD, PO Box 9902, San Diego, 92109. (619) 276-3616.

September 23-27—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD. Monday-Friday. 13-33 hrs. Fee: $215-440.

September 26-28—**1985 Pacific Occupational Safety and Health Conference** at Le Baron Hotel, San Jose. Thursday-Saturday. Contact: Duke Hughes, POSH '85, PO Box 4420, Santa Clara, CA 95054. (408) 988-1111.

September 27-28—**40th Annual Merritt Hospital Medical Staff Seminar: Medicine, 1985.** Samuel Merritt Hospital at Kaiser Center and Merritt Hospital, Oakland. Friday-Saturday. 10 hrs. Fee: $20. Contact: Patricia R. Napp, Med. Staff Support Services, Merritt Peralta, Hawthorne Ave. & Webster St., Oakland, CA 94609. (415) 655-4000.

September 28-29—**The Skin From A to Z.** UCSF at Holiday Inn, Napa Valley. Saturday-Sunday.

September 29-October 2—**Symposium on Prevention of Osteoporosis.** University of Hawaii at Westin Ilikai Hotel, Honolulu. Sunday-Wednesday. 13.5 hrs. Fee: $300. Contact: Dr Philip Ross, Osteoporosis Center, Kuakini Medical Center, 347 N. Kaukini St., Honolulu, HI 96817. (808) 547-9578.

IDAHO

July 19-25—**Up-to-Date Cardiac Therapy.** Salmon River, Idaho White Water Rafting. Friday-Thursday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

July 21-28—**Computers in Professional Practice and Financial Planning.** Sun Valley. One week. 24 hrs. Cat I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, PO Box 2668, Boise 83701. (208) 344-7888.

August 3-9—**Selected Topics in Wilderness and Environmental Medicine.** Mt. Bike Tour, McCall, Idaho. Saturday-Friday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 15-17—**Sun Valley Emergency Medical Conference.** Sun Valley. Thursday-Saturday. Followed by a float trip on the Middle Fork of the Salmon River, August 18-20. Sponsors: Idaho Emergency Medical Services System; Idaho Chap, American College of Emergency Physicians; Idaho Chap, Emergency Nurses Assn; Idaho Committee on Trauma, American College of Surgeons; Rural Area Model System. Contact: Idaho EMS System, 450 W State St., Boise 83720. (208) 334-4245.

August 15-21—**Effective Diagnosis and Treatment of Infectious Diseases.** Middle Fork of the Salmon River, Idaho White Water Rafting. Thursday-Wednesday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

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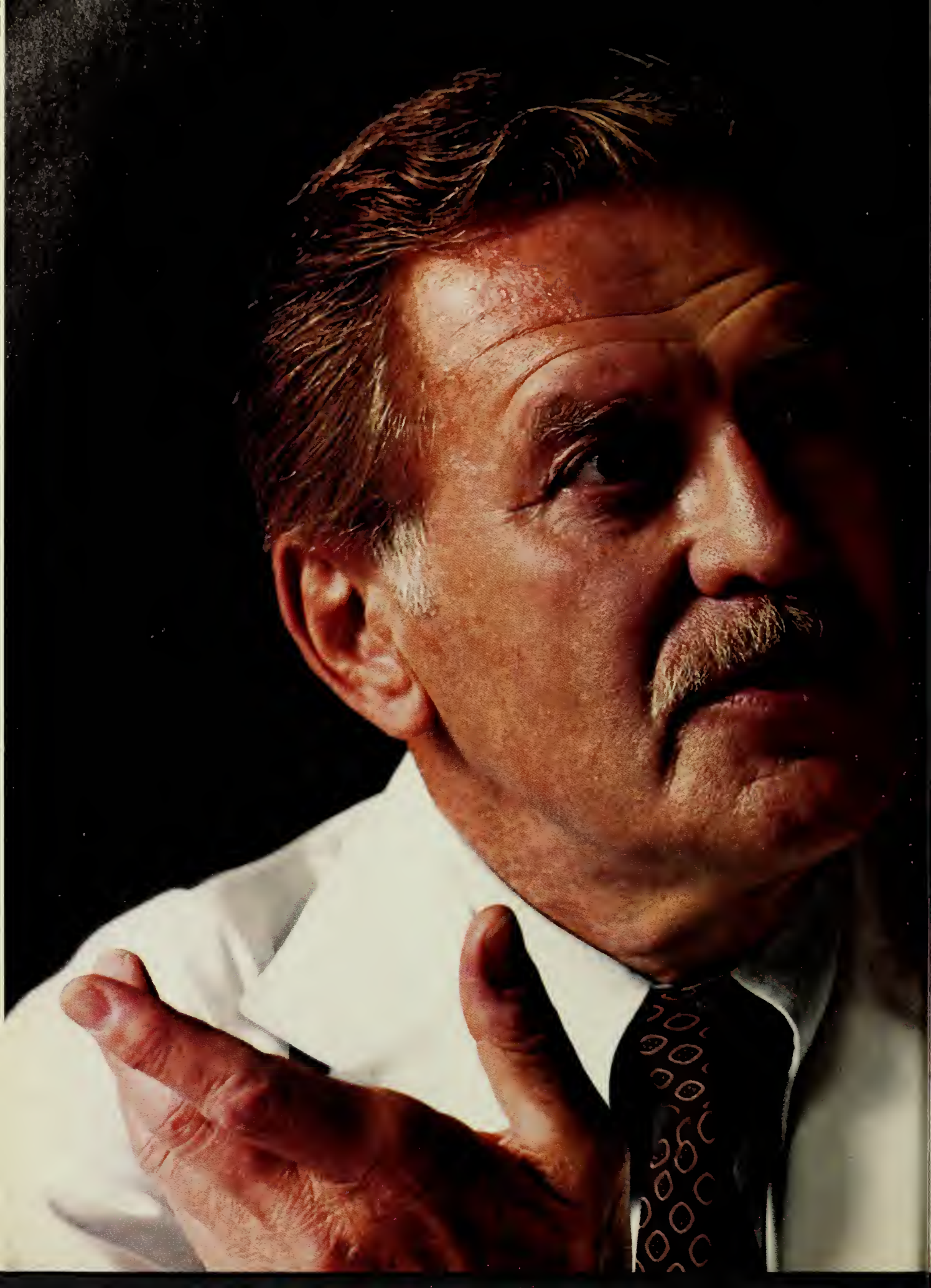

"When it comes to cardiovascular medicine, I like to know exactly what my patients are swallowing."

There are doctors who say that generic drugs have a place in their practice—but not necessarily in the treatment of serious or potentially life-threatening disease. And when they consider that the average patient pays only about 45¢ a day for INDERAL (propranolol HCl) Tablets, there's not much left to discuss.

When it's INDERAL Tablets you want for the treatment of hypertension, angina, arrhythmias, or post-MI patients, make sure you specify "Dispense As Written" (DAW), "Do Not Substitute," or whatever is required in your State. That way, you'll know exactly what your patients will get.

Please see next page for brief summary of prescribing information.

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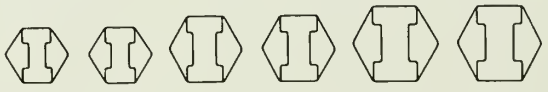

10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System. Lightheadedness, mental depression manifested by insomnia, lassitude, weakness fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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New York, N Y. 10017

(Continued from Page 31)

August 22-25—**Intermountain Dermatology Society.** Red Fish Lake Lodge, Idaho. Thursday-Sunday. 9½ hrs. Sponsor: University of Utah. Contact: C. David Hansen, MD, (801) 321-1100.

September 8-14—**Up-to-Date Cardiac Therapy.** Middle Fork of the Salmon River, Idaho White Water Rafting. Sunday-Saturday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

October 12-18—**Effective Diagnosis and Treatment of Infectious Diseases.** Salmon River, Idaho Sports Fishing. Saturday-Friday. 24 hrs. Cat I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

October 3-5—**Montana Medical Association Annual Meeting.** Outlaw Inn, Kalispell. Thursday-Saturday. Contact: NNA, 2012 11th Ave., Ste. 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 15-18—**28th Annual Ruidoso Family Practice Seminar.** Mescalero. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I and AAFP Prescribed Credit. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

September 12-14—**Concepts and Controversies in Perinatal Care.** Albuquerque. Thursday-Saturday. 13 hrs. AMA Cat. I. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

October 4-5—**Ophthalmology for Primary Care Physicians.** Albuquerque. Friday-Saturday. Marriott Hotel. 10 hrs. AMA Cat. I. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

October 10-12—**New Mexico Cancer Symposium: Current Concepts in Cancer Management for Practicing Physicians.** Albuquerque. Thursday-Saturday. La Posada de Albuquerque. 15 hrs. AMA Cat. I. Contact: St Joseph Cancer Center, Albuquerque 87102. (505) 848-8000.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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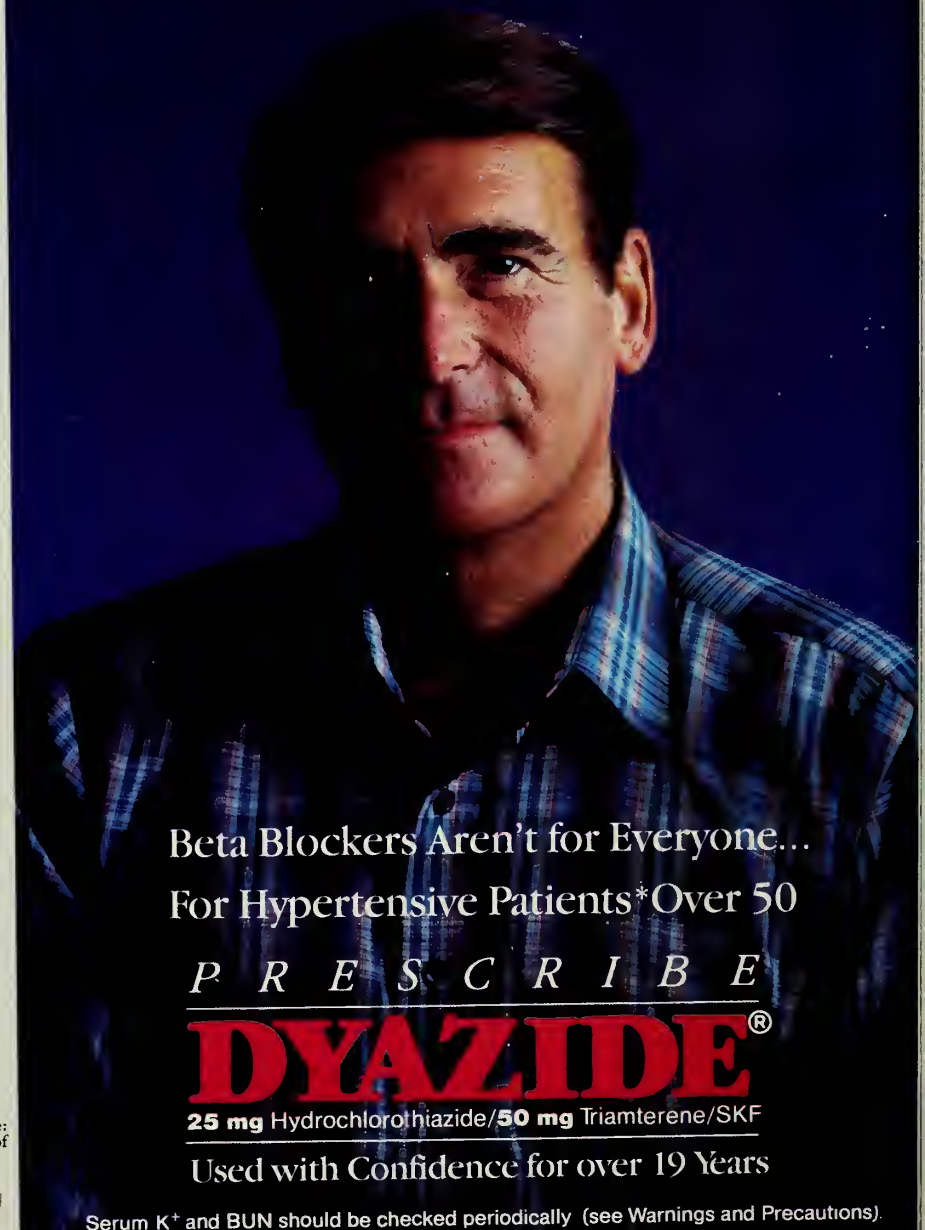
In Hypertensives Over 50, Diuretics Are Preferred

The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics as the favored monotherapy in patients over 50 years of age, regardless of sex or race.



Beta Blockers Aren't for Everyone...

For Hypertensive Patients*Over 50

P R E S C R I B E

DYAZIDE®

25 mg Hydrochlorothiazide/**50 mg** Triamterene/SKF

Used with Confidence for over 19 Years

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: **'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

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Clinical Investigation

Epidemiologic and Clinical Factors of *Chlamydia trachomatis* in Black, Hispanic and White Female Adolescents

RONALD M. EAGAR, MD; ROBERTA K. BEACH, MD, MPH; ARTHUR J. DAVIDSON, MD, *and* FRANKLYN N. JUDSON, MD, *Denver*

Rates of genital infection with Chlamydia trachomatis, Neisseria gonorrhoeae *and* Trichomonas vaginalis *were determined prospectively in 396 sexually active female adolescents from three ethnically different urban teen clinics. The organisms were identified respectively in cultures of specimens from 21%, 7% and 6% of all adolescents; 28%, 16% and 20% of blacks; 23%, 4% and 2% of Hispanics, and 14%, 2% and 1% of whites.* C trachomatis *was identified in specimens from 27% of pregnant adolescents and from 42% of adolescents who had gonorrhea or trichomoniasis.*

Of 85 Chlamydia*-positive adolescents, 47 (55%) were asymptomatic. Physical findings significantly associated (*P < .001*) with chlamydial infection were vaginal discharge, cervical inflammation and mucopurulent endocervical discharge. Not significantly associated (*P > .05*) with* Chlamydia *were the use of oral contraception or symptoms of lower abdominal pain, vaginal discharge or dysuria. Because in sexually active female adolescents* C trachomatis *is three times more common than* N gonorrhoeae, *care givers need to consider routine screening or epidemiologic treatment (or both) for both pathogens.*

(Eagar RM, Beach RK, Davidson AJ, et al: Epidemiologic and clinical factors of *Chlamydia trachomatis* in black, Hispanic and white female adolescents [Clinical Investigation]. West J Med 1985 Jul; 143:37-41)

Chlamydia trachomatis has become the most common sexually transmitted pathogen of female adolescents.[1-3] Diseases associated with *Chlamydia* include cervicitis, salpingitis and its complications and the acute urethral syndrome in women; urethritis and epididymitis in men, and inclusion conjunctivitis and pneumonia in neonates.[4]

An estimated 10 million teenage women in the United States are sexually active.[5] Chlamydial infection rates of 8% to 26% have been reported for selected adolescent populations but vary considerably according to age, ethnicity, sexual activity, geography and other factors.[2,3,6-8] Unfortunately, most clinical correlates of infection have been unreliable, while laboratory cultures for *Chlamydia* are costly and not yet widely available; diagnosis is often presumptive. Finally, only limited information has been published on chlamydial infection rates in pregnant adolescents.[3,8]

We therefore undertook a study to (1) determine the prevalence rates of *C trachomatis, Neisseria gonorrhoeae* and *Trichomonas vaginalis* in pregnant and nonpregnant black, Hispanic and white female adolescents who attended one of three urban teen clinics, and (2) identify patient history or physical findings significantly associated with chlamydial infection.

Methods

Patients

Patients were sexually active female adolescents who received care at one of three Denver Department of Health and Hospitals adolescent clinics. The adolescent clinics at the Eastside Neighborhood Health Center (from which 148 of our patients came) and the Westside Neighborhood Health Center (149 patients) offer comprehensive primary care to

From the Disease Control Service (Drs Davidson and Judson) and the Neighborhood Health Program (Drs Eagar and Beach), Denver Department of Health and Hospitals, and the Departments of Pediatrics (Drs Eagar and Beach), Medicine, Division of Infectious Diseases (Dr Judson), and Preventive Medicine (Drs Davidson and Judson), University of Colorado Health Sciences Center, Denver. The Centers for Disease Control, Division of Sexually Transmitted Diseases, Atlanta, provided funding support for *Chlamydia* cultures.

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Reprint request to Franklyn N. Judson, MD, Disease Control Service, 605 Bannock Street, Denver, CO 80204-4507.

predominantly low-income black and Hispanic young people. The Denver Free Teen Clinic (99 of our patients), located in the Denver Public Health Department, offers confidential services limited to contraception and pregnancy testing and serves primarily white teenagers from low- to middle-income families.

Any clinic patient who received a pelvic examination between October 1983 and March 1984 was screened for enrollment in this study. Women were included if they were 12 through 18 years of age, sexually active, had not taken any antibiotics or used any intravaginal preparation (spermicide, douche or suppository) within the previous 28 days and had not been a prior study participant.

Data Collection

To maintain consistency in collecting data, the study staff from the three clinics attended a joint training session on the study protocol and their work was continually monitored by one of the principal investigators. A standardized data entry form was used for the history and physical examination. Historical data included age, race, family income, reason for encounter, specific symptoms, contraceptive use, obstetric and gynecologic history, sexual history and previous episodes of sexually transmitted disease. Abdominal and pelvic examinations were carried out with special attention to vaginal discharge (profuse creamy or frothy discharge in vault), cervical inflammation (erythematous, eroded or friable cervix), mucopurulent discharge from the cervical os and pelvic tenderness. Endocervical cultures for *N gonorrhoeae* and *C trachomatis* and a vaginal wet mount for *T vaginalis* were done on specimens from all subjects.

Laboratory Techniques

Laboratory specimens were taken by the examining clinician using standardized techniques. Before the bimanual examination and after inserting a clean unlubricated speculum, specimens for *N gonorrhoeae* were obtained by inserting two consecutive cotton-tipped swabs in the endocervical canal, allowing 10 seconds for adsorption and inoculating the swabs 180 degrees apart onto a modified Martin-Lewis medium. Media were processed in the clinic's usual manner.[9] Presumptive identification of *N gonorrhoeae* consisted of typical colony morphology, a positive oxidase test and Gram-negative diplococci on a Gram's stain.

The specimen for *C trachomatis* was then collected by inserting a cotton-tipped swab into the endocervical canal with a vigorous rotary motion. Swabbed specimens were swirled and expressed into one-dram vials containing glass beads and 1 ml of transport media (0.2 mol per liter sucrose to 0.02 mol per liter phosphate, 4 μg per ml amphotericin B, 10 μg per ml gentamicin), which were immediately placed in an ice bath and transported the same day to the Disease Control Service Laboratory.* If specimens could not be inoculated into cells within 24 hours, they were stored at −70°C.

Cultures were done by vortexing the specimen and inoculating 0.2-ml aliquots into each of three one-dram glass vials containing a 12-mm coverslip coated with a confluent monolayer of McCoy cells (M.A. Bioproducts, Walkersville, Md). Vials were centrifuged at 3,000 g for one hour at 25°C to 35°C, the inoculum discarded, the monolayer rinsed once and 1 ml of medium added to each vial. Cultures were incubated for 48 to 72 hours at 30°C to 35°C. Coverslips were fixed in methanol, stained with iodine and examined for intracytoplasmic inclusions.

A cotton-tipped swab specimen of the posterior vaginal puddle was mixed with physiologic saline on a glass slide and viewed by light microscopy. Trichomoniasis was diagnosed by the presence of typical, motile, pear-shaped, flagellated protozoa.[10]

Statistical Methods

Quantitative analysis for possible risk factors was done using the χ^2 method.[11] Comparisons of rates of *C trachomatis* by race were done based on methods described by Rosner.[12] Because of the small numbers, Fisher's exact test was used to evaluate associations of *C trachomatis* and trichomoniasis.

Results

From October 1983 through March 1984, 396 female adolescents were enrolled in the study. The mean age was 16.2 years (range, 12 to 18). The principal reasons for clinic visits were the following: family planning, 192 (48%); genitourinary symptoms, 85 (21%): pregnancy diagnosis and pre-

Chlamydia cultures were prepared by Josephine Ehret.

TABLE 1.—*Obstetric and Gynecologic Characteristics of 396 Female Adolescents by Ethnic Group*

Characteristic	Ethnic Group							
	Black N=99		Hispanic N=166		White N=126		All N=396*	
Mean age (yr)	16.1		16.3		16.2		16.2	
Mean age menarche (yr)	12.4		12.2		12.5		12.4	
Mean age first intercourse (yr)	14.5		15.0		14.9		14.8	
Currently pregnant (% of N)	25	(25)	52	(31)	9	(7)	86	(22)
Birth control method (% of N)†								
None‡	64	(65)	116	(70)	77	(61)	259	(65)
Oral contraceptives	29	(29)	36	(22)	35	(28)	102	(26)
Condoms	2	(2)	10	(6)	13	(10)	26	(7)
Intrauterine device	3	(3)	3	(2)	0	(0)	6	(2)
Other§	1	(1)	1	(1)	1	(1)	3	(1)

*Includes 2 Native American and 3 Southeast Asian girls.
†The percentages add up to more than 100 due to rounding off of numbers.
‡Includes pregnant women.
§Patients using spermicides were excluded from the study.

natal care, 80 (20%); postpartum care, 32 (8%); examination for sexually transmitted diseases, 9 (2%), and other, 10 (3%). Multiple reasons for visits were accepted. The study population included 99 (25%) blacks, 166 (42%) Hispanics, 126 (32%) whites and 5 (1%) others. Obstetric and gynecologic characteristics of the study population are given in Table 1. There were no significant differences by ethnic group except for a lower rate of pregnancy (7%) in white patients.

C trachomatis was identified in specimens from 21% (85/396) of all adolescent women (Table 2). The prevalence rate in black teenagers was twice as high as in whites (28% versus 14%, $P<.001$) and was significantly higher than in Hispanics (28% versus 23%, $P<.008$). Hispanics also had significantly higher rates than whites ($P<.001$). *N gonorrhoeae* was cultured in specimens from 7% (26/396) of all teenagers, but from 16% of blacks compared with 4% of Hispanics and 2% of whites. *T vaginalis* was seen in 6% of all women; 20 of 24 cases were in blacks, who had an infection rate of 20% compared with 2% in Hispanics and 1% in whites. Coexistent infection with *C trachomatis* was identified in 11 of 26 (42%) patients with gonorrhea and 10 of 24 (42%) with trichomoniasis. Nearly 27% (106/396) of all subjects had at least one of these three organisms.

A total of 86 (22%) patients were pregnant, of whom 23 (27%) had *Chlamydia*, 4 (5%) had gonorrhea and 7 (8%) had *T vaginalis*. When controlled for ethnicity, the rate of *Chlamydia* infection in pregnant teens was not significantly different ($P<.25$) from that in nonpregnant teens.

Of 85 patients with chlamydial infection, 38 (45%) presented with genitourinary symptoms (discharge, dysuria or abdominal pain). Symptoms reported after direct questioning and physical findings from pelvic examinations were compared with culture results (Table 3). No symptom, including the prevalent vaginal discharge, was significantly associated with a positive chlamydial culture. *C trachomatis* was identified in specimens from 38% of 113 women with the sign of vaginal discharge, 50% of 38 with cervical inflammation and 45% of 51 with mucopurulent endocervical discharge, each of which represents a significant association ($P<.001$). However, 30 of 85 (35%) did not have any of these three clinical indicators of infection. Pelvic tenderness on bimanual examination was not significantly associated with cultures positive for *Chlamydia* ($P<.9$).

Six patients had a clinical diagnosis of acute pelvic inflammatory disease at the initial visit. In one, culture was positive for *N gonorrhoeae*; in two, cultures were positive for *C trachomatis*, and three had negative cultures. The only patient diagnosed as having acute perihepatitis had a positive *Chlamydia* culture. No significant positive association was found between chlamydial infection and the use of oral contracep-

TABLE 2.—*Comparative Rates of Infection With* Chlamydia trachomatis *(CT),* Neisseria gonorrhoeae *(GC) and* Trichomonas vaginalis *(TV) in 396 Female Adolescents, by Ethnic Group*

Infecting Organism	Ethnic Group: Black (N=99) No. Positive	(%)	Hispanic (N=166) No. Positive	(%)	White (N=126) No. Positive	(%)	All (N=396)* No. Positive	(%)
CT+†	28	(28)	38	(23)	18	(14)	85	(21)
GC+	16	(16)	7	(4)	3	(2)	26	(7)
TV+	20	(20)	3	(2)	1	(1)	24	(6)
CT+/GC−	23	(23)	32	(19)	18	(14)	74	(19)
CT−/GC+	11	(11)	2	(1)	2	(2)	15	(4)
CT+/GC+	5	(5)	5	(3)	1	(1)	11	(3)
None	50	(50)	121	(73)	104	(83)	290	(73)

*Includes 2 Native American and 3 Southeast Asian girls.
†See Results section for statistical significance.

TABLE 3.—*Significance of Association Between Clinical and Laboratory Findings and Infection With* Chlamydia trachomatis *(CT) in 396 Female Adolescents*

Clinical/Laboratory Finding	CT+ N=85 Finding	(%)	CT− N=313 Finding	(%)	Significance P Value*	Relative Risk
Symptoms						
Vaginal discharge	28	(33)	96	(31)	<.75	1.08
Abdominal pain	8	(9)	28	(9)	<.90	0.75
Dysuria	5	(6)	32	(10)	<.25	0.61
Signs						
Vaginal discharge	43	(51)	70	(22)	<.001	1.88
Cervical inflammation	19	(22)	19	(6)	<.001	2.73
Cervical discharge	23	(27)	28	(9)	<.001	2.52
Tenderness on bimanual examination	10	(12)	40	(13)	<.90	0.93
Laboratory						
Neisseria gonorrhoeae	11	(13)	15	(5)	<.01	2.13
Trichomonas vaginalis	10	(12)	13	(4)	=.006†	2.17

*Analysis by χ^2.
†Analysis by Fisher's exact test.

tives ($P < .25$), a history of gonococcal infection ($P < .95$), sexual contact within seven days ($P < .5$), chronologic age, age at first intercourse or years sexually active.

Discussion

The actual prevalence of *C trachomatis* in American teenagers is not known because true random sampling of large adolescent populations has not been done. Our study and others previously reported have focused on sexually active female adolescents, primarily from lower income families, who underwent pelvic examination at either comprehensive or gynecologic adolescent clinics. Even in these more limited populations, rates of *C trachomatis* infection have varied: 22% in Cincinnati,[6] 8% in Oklahoma City,[7] 15% in San Francisco,[2] 10% in Brooklyn[8] and 26% in Baltimore.[3] Our overall identification rate of 21% confirms that *C trachomatis* is a dominant pathogen in sexually active Denver urban teenagers.

Identification rates of both *C trachomatis* and *N gonorrhoeae* from black and Hispanic teens were higher than in previous studies of adolescents. Our sample of 166 Hispanic teens is the largest yet reported. *Chlamydia* infection was identified in 23%, compared with 14% found by Shafer and co-workers[2] and 6% by Golden and associates.[8] Likewise, the *Chlamydia* infection rate of 28% in black teens was higher than the 7% to 23% rates previously reported. Although minority teens are at significantly greater risk for *C trachomatis* infection than white teens, important confounding variables to race and ethnicity need further study. These may include geography, socioeconomic status, sexual activity patterns, the use of health care resources and laboratory techniques.

Pregnant indigent adolescents have been reported to have a high prevalence of *Chlamydia* infections,[3,13-15] which our rate of 27% confirms. If *C trachomatis* is untreated in the mother, Frommell and colleagues[13] found that perinatal transmission will occur in about 61% of neonates; inclusion conjunctivitis will develop in 73% and interstitial pneumonia in 18%. In addition, unconfirmed reports have associated maternal chlamydial infection with higher rates of spontaneous abortion, prematurity and postpartum endometritis.[14,15] Thus screening for *C trachomatis* would seem to be an important addition to routine prenatal care.

Because *Chlamydia* cultures are not widely available, investigators have attempted to identify symptoms or signs that might be reliable indicators of the presence of infection. Our study shows that no clinical symptom, including vaginal discharge, abdominal pain or dysuria, is reliably associated with chlamydial infection in female adolescents. Furthermore, 55% of our patients with *Chlamydia* infections were asymptomatic, similar to rates of 45% to 86% reported by others.[2,3,6-8]

We did find statistically significant ($P < .001$) associations between patients with chlamydial infection and the findings on genital examination of vaginal discharge, cervical inflammation and mucopurulent cervical dischage. Mucopurulent cervical dischage may be the most significant clinical marker of *C trachomatis*. Our finding *Chlamydia* in specimens from 23 of 51 patients (45%) with endocervical discharge is consistent with the recently published study of Brunham and co-workers,[16] who identified *C trachomatis* in specimens from 20 of 40 women (50%) who had mucopurulent cervicitis. They propose that mucopurulent cervicitis be diagnosed by the following more objective criteria: visualization of yellow mucopurulent endocervical secretions on a white swab or the presence of ten or more polymorphonuclear leukocytes per high power field (×1,000) in a satisfactory Gram-stained smear. In most published studies of adolescents, owever,including this report, cervical abnormalities have been either unmentioned or variously reported as inflammation, rosion, ectopy or friability, so that comparison of findings is not possible. Future studies need uniform criteria for describing cervical findings.

Presumptive treatment of all adolescents with any one of the significantly associated physical markers of chlamydial infection—that is, vaginal discharge, cervical inflammation or mucopurulent cervical discharge (or all of these)—would result in the correct treatment of 50 of 85 (59%) infected patients and the unnecessary treatment of 108 of 311 (35%) uninfected patients. Whether or not this approach would be viewed as a cost-effective control effort or inappropriate treatment is a value judgment.

The frequent coexistence of *N gonorrhoeae* and *C trachomatis* infection has been well enough documented[17-19] that the Centers for Disease Control now recommend that patients with *N gonorrhoeae* be treated with a regimen that is also effective against *Chlamydia*.[20] Our finding that 42% of patients with gonorrhea also had cultures positive for *Chlamydia* supports this recommendation. *T vaginalis* is an easily diagnosed sexually transmitted organism that can serve as a marker of sexual activity.[10] It was found in 6% of our subjects, of whom 42% also had cultures positive for *Chlamydia* ($P = .006$), a finding that is comparable to the study of Shafer and colleagues[2] in which 32% of subjects with trichomonads on Papanicolaou smears had cultures positive for *Chlamydia* ($P = .009$). This relationship needs further investigation but suggests that teenaged girls with trichomoniasis should either be screened for *Chlamydia* or receive presumptive treatment.

Implications

This large study confirms that *C trachomatis* is the most common sexually transmitted pathogen in sexually active urban adolescents. American teenagers with chlamydial infections have not been studied longitudinally to determine morbidity, but the many possible complications raise serious concern. In Scandinavian studies, *C trachomatis* has been associated with 40% to 60% of laparoscopically proved salpingitis.[21] Westrom estimates that in the 15- to 24-year-old age group, 9.4% will become infertile after one episode of salpingitis and 51.6% after the third episode.[22] In his studies, estimates of the risk for ectopic pregnancy escalate from 1 in 300 without salpingitis to 1 in 24 following salpingitis. *Chlamydia* may well play some etiologic role in the tripled incidence of both infertility and ectopic pregnancy reported in the United States during the past decade.[16,21,23] These sequelae, along with the immediate morbidity associated with the enlarging spectrum of chlamydial diseases in patients, partners and offspring, represent a major public health concern reminiscent of gonorrhea in the late 1960s and early 1970s. The methods used to control *N gonorrhoeae*—widespread routine culturing, reporting to public agencies, aggressive treatment of contacts—should be considered for *Chlamydia*.

At present, a culture is the only reliable means of diagnosing *C trachomatis*, but cultures are expensive, labor intensive, require 72 hours for results and are not widely available. Screening tests based on antigen detection systems are promising but require further study.[24]

Until more adequate diagnostic tests for *Chlamydia* are available, we suggest the following guidelines to care givers of sexually active adolescents:

- For diseases consistently and significantly associated with chlamydial infection (mucopurulent cervicitis, gonorrhea, salpingitis and distal urethritis in women; gonococcal and nongonococcal urethritis and epididymitis in men), treat with an antimicrobial regimen that includes treatment for *C trachomatis*.
- In women with trichomoniasis or vaginal discharge of any cause, maintain a high index of suspicion for chlamydial infection and consider using treatment effective against *C trachomatis*.
- If chlamydial cultures are available, take specimens for culture from any sexually active teenaged girl (particularly if pregnant) who would not otherwise receive treatment for *Chlamydia* on the basis of risk factors of infection noted above.
- Simultaneously treat partners of patients with known or suspected chlamydial infection with effective treatment.
- Educate adolescents about the risks and sequelae of sexually transmitted diseases, including the seldom-heard-of *Chlamydia* infections.

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Current Concepts in Endometriosis

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There are no conclusive data available on the incidence or prevalence of endometriosis, yet the notion persists that the frequency of cases has dramatically risen in western societies during the past 25 years. Race, familial predisposition, reproductive history, socioeconomic status, personality type and a historical drop in age at menarche have been posited as risk factors for the complex and as-yet-unclear epidemiology of this disorder.

The epidemiology of endometriosis is constrained by the difficulty of the diagnosis. Several analytic concepts from epidemiology, however, could be profitably used to further our knowledge of endometriosis. Included are the case-control study, survival and life-table analyses and correlations of psychologic traits with susceptibility to development of the disease. Though none of these techniques is original or without potential for bias, they may be underutilized in solving the conundrum of endometriosis.

(Molgaard CA, Golbeck AL, Gresham L: Current concepts in endometriosis. West J Med 1985 Jul; 143:42-46)

Endometriosis is a crippling and enigmatic disorder that frequently coexists with severe pelvic pain and infertility. It is characterized by the presence of tissue resembling endometrium, the mucous membrane lining the uterus, in various abnormal locations including the uterine walls, ovaries or extragenital sites. Endometriosis was first brought to the attention of the medical community by Rokitansky in 1860. Between that time and Sampson's contributions to knowledge of this disease in the 1920s, fewer than 20 cases of endometriosis were reported in the literature.[1] Thereafter, reported cases have dramatically increased in western societies. The onset of endometriosis during the reproductive years may prevent childbearing and often necessitates a hysterectomy or castration. The exact cause of infertility in patients with this disease—twice the rate of that found in the normal population—is not known.

The epidemiology of endometriosis is not well defined. The purpose of this review is to provide a summary of current concepts contributing to our population-level knowledge of this disease and to promote future analyses using epidemiologic tools in the study of endometriosis.

Salient Clinical Features

Etiology

The pathogenesis of endometriosis is unclear. The most popular notion is that it is caused by implantation of endometrial cells, although why endometrial cells should be implanted at abnormal sites is a mystery. Marik[2] has reviewed the numerous theories of etiology and made the point that no one theory explains the presence of endometriosis in all of the unusual locations where it has been found. He categorized the causative theories into three main groupings: transport, mutation and a combination of these. Transport could occur by spontaneous implantation, surgical or iatrogenic transplantation, metastasis via lymphatic channels or blood vessels or by direct extension to organs immediately adjacent to the uterus. Mutation could result from coelomic metaplasia, ovarian metaplasia, dedifferentiation or from activation of embryonic rests by the cyclic female hormonal stimuli to form aberrant endometrial tissue.

A recent genetic study indicated multifactorial inheritance: 7% of first-degree relatives of the index cases were affected compared with 1% of a control group consisting of relatives of the patients' husbands.[3] This control group was chosen because they were considered similar to the general population in terms of life-style, socioeconomic status, professional goals and age. A tendency for familial aggregation of cases has long been noted, though the inherited endocrinologic, enzymatic or chemical mechanisms are unknown. None of these causes is more powerful than the others in explaining the posited association with infertility.

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Symptoms

Endometriosis may be acute or chronic and the site of the disorder often affects the type and degree of symptoms. Although endometriosis occurs most frequently in the pelvic region, on rare occasions it has been located in such distant sites as the gallbladder, kidneys, spleen, lungs and skin. The four cardinal features of the disease are infertility, dysmenorrhea and pelvic pain, dyspareunia and menstrual problems.[4] Differential diagnoses include adenomyosis, pelvic inflammatory disease, nonspecific adhesions and ovarian carcinoma.[5]

Patients with massive endometriosis may be devoid of symptoms, whereas a woman with only minor endometriotic involvement may be incapacitated with dysmenorrhea or pelvic pain. Pelvic pain may be due to direct action of endometriosis on local nerve endings or to impaired function of involved or adjacent organs. In either case, a definitive diagnosis of endometriosis cannot be made without direct visualization, either by laparotomy or laparoscopy.[6] Determining the incidence and prevalence of endometriosis has been severely constrained in the past by the difficulty of the diagnosis.

Treatment

Choice of treatment depends on the situation of an individual patient. The three major options are organ excision, conservative surgical treatment or medical treatment.[7] Organ excision involves removing the internal pelvic reproductive organs, that is, the source of the endometriosis (the uterus) and the hormonal stimulus for its growth (the ovarian hormones), by a hysterectomy and bilateral salpingo-oophorectomy. Conservative surgical removal consists of excising tissues with endometriosis. Medical treatment attempts to end menstruation through the use of oral contraceptives, progestogens (to cause pseudopregnancy) or danazol (to cause pseudomenopause). A recent study by Shaw[8] points to intranasal treatment with buserelin acetate, an analog of natural luteinizing hormone-releasing hormone, which blocks release of pituitary gonadotropins, in turn suppressing ovarian steroid production. Comparison of treatment alternatives is extremely difficult because of the lack of isomorphism between symptoms and degree of involvement; the tendency of endometriosis to regress, especially if pregnancy occurs, and the lack of a universally accepted classification system for endometriosis. The last affects not only the comparison of studies of treatment efficacy, but also the interpretation of frequency of occurrence estimates by different researchers.

Recurrence of endometriosis is variable and depends on the type of intervention involved. It cannot be predicted by the severity of the endometriosis.[9]

Epidemiologic Features

Information concerning the prevalence of endometriosis is incomplete, though pelvic endometriosis has been reported in 5% to 15% of all women having pelvic operations.[10] Corson[11] has suggested that it occurs less in England and Australia than in the United States. However, the notion persists that the incidence is increasing,[12] supported by increased case findings in recent decades. Concomitantly, a constellation of epidemiologic beliefs has evolved concerning endometriosis, the most general of which is that endometriosis is a product of modern civilization. This theory is based on the supposed infrequency of endometriosis among blacks and Asians.[13-15]

A second notion is that of an endometriosis personality type, Kistner[16] describing this as the interaction of body type and psychic demeanor. The main characteristics involve being mesomorphic but underweight, having above-average intelligence, a higher than normal anxiety level, egocentrism and a need for perfection.

Age at diagnosis, in lieu of age at onset, is usually the third or fourth decade. Absence of the condition in girls before menarche is explained by the fact that endometriosis requires fluctuating levels of estrogen and progesterone for its initiation and spread. Endometriosis, however, may be symptomatic after menopause if there is a resurgence of endogenous hormonal stimulation or if the use of exogenous hormones stimulates the endometriosis.[17]

In terms of reproductive history, the condition is believed to be more common in women who delay their first pregnancy and less common in the highly parous.[18] The lack of opportunity for retrograde menstruation among the latter group has been offered as a possible explanation.

Related to reproductive history is the usually higher-than-average socioeconomic status of women with this condition. Women from high socioeconomic groups tend to have fewer and later pregnancies than those from lower socioeconomic groups.[19] The position has been taken that the incidence is lower in blacks not because of race, but because of endemic poverty among a large proportion of the black population.[20] Poverty could create an apparent differential in disease occurrence among racial groups because of differential access to specialized medical care and the existence of a prejudicial diagnostic posture based on what is "known" about racial susceptibility to endometriosis.

Association With Infertility: Spurious or Real?

Support for the association between endometriosis and infertility is based on clinical data and has been well accepted. The argument has been based on the assumption that infertility characterizes 15% of the general female population of reproductive age, and that this increases to 30% to 40% in the population of patients with endometriosis.[5] Further support for the association involves surgical series, where subsequent pregnancy rates of 40% to 73% occurred among patients with endometriosis (and no other cause for infertility) following conservative surgical treatment.[21]

It is possible, however, that the apparent relationship between infertility and endometriosis is an example of sampling bias related to the frequency with which a laparotomy or laparoscopic examination is used to evaluate cases of infertility. Few studies have reported if laparoscopy was done as a routine procedure in the evaluation of infertile patients when physical examination had shown no other positive findings, or what signs and symptoms are considered sufficient to warrant laparoscopy. Information supporting the association of endometriosis and infertility has been considered inconclusive.[22]

Given that the association exists, it has been held in the past that endometriosis does not cause infertility unless it is severe enough to alter tubo-ovarian function. If both tubes and ovaries are involved in the process and peritubal adhesions are present, tubal dysfunction could impair ovum pickup. The increased use, however, of laparoscopy in infertility studies

has revealed the coexistence of minimal endometriosis (peritoneal involvement only) and infertility. It is unclear how the mild form of endometriosis can alter the process of conception, and this fact has led to the suggestion that minimal endometriosis may be the effect rather than the cause of infertility.[23] Yet evidence for the efficacy of conservative surgical treatment in cases of even mild endometriosis has continued to accumulate. Buttram[21] evaluated the effect of conservative operations on 56 patients with mild endometriosis as the only known cause of infertility: 78% of these women had been trying to conceive for two or more years. Within 15 months after an operation, 73% were pregnant. His cautious conclusion was that the surgical procedure somehow altered the pelvic environment (enzymatic, chemical, immunologic) so that the effect of the endometriosis on fertility was altered. In contrast, a subsequent study[24] based on a life-table analysis of conceptions concluded that mild endometriosis does not necessarily interfere with fertility.

One current theory explaining the relationship between endometriosis and infertility is immunologic. It proposes that ectopic or abnormal endometrium is recognized differently by the immune system, which launches an antibody response to the condition that may affect the patient's fertility. An autoimmune response is triggered in some women when endometriotic tissue is phagocytized and absorbed by the host. This might cause rejection of an embryo or disrupt sperm transport.[25] A second theory posits that the ovum may be attracted to any endometrium wherever it is located. Evidence for this position involves reports of abdominal pregnancies in areas of endometriosis. Given that the distance between the ovary and normal endometrium is greater than that between the ovary and the endometriosis, a patient's fertility could again be impaired. A third theory, which is the subject of controversy, is that of the "luteinized unruptured follicle" syndrome.[26] In brief, this hypothesis posits a situation wherein the ovarian follicle fails to release the ovum despite proceeding through the other changes associated with ovulation. This assumes that retrograde menstruation is actually a common event, that endometrial cells do not implant as frequently as they might and that the failure to implant can be explained by steroid hormone concentrations in peritoneal fluid. Women with complete ovulatory cycles have very high steroid hormone (progesterone) concentrations after ovulation, which would prevent growth and development of endometrial cells by rendering them inactive, whereas women with unruptured luteinized follicle syndrome do not.[25] The result would be infertility and endometriosis, but infertility would be the cause of endometriosis, as mediated through the unruptured luteinized follicle syndrome, and not the result. This hypothesis has been challenged as being very inaccurate.[27] The most general criticism has been that identifying the stigma, or site of the ovum release, by laparoscopic examination of the surface of the luteal structure is fraught with potential for error. If the stigma is absent, luteinized unruptured follicle is presumed, but recognizing the stigma depends on the experience of the laparoscopist, the time in the cycle and other idiosyncratic factors. This compromises any examination of the frequency of stigmata in relation to the varying severity of endometriosis.

A fourth theoretical position[28] claims no causal relationship to date involving the role of prostanoids in the peritoneal cavity and infertility among endometriosis patients. A fifth theory points to the high concentrations of peritoneal macrophages found in patients with this disease. Attracted perhaps by irritants in the oviduct, monocytes migrate to the peritoneal region and differentiate into macrophages, possibly resulting in sperm phagocytosis.

Of the major epidemiologic research designs, a case-control design is perhaps the only appropriate choice for the study of the association between endometriosis and infertility. A case-control study was recently undertaken at the Mayo Clinic to compare the presence of endometriosis in infertile and fertile populations as visualized by laparoscopy.[29] The medical records retrieval system of the Rochester Epidemiology Program Project was used to conduct the study.[30] The records of 100 Mayo Clinic referral patients who had been evaluated for infertility by means of laparoscopy between 1970 and 1979 were retrieved. Operative reports were reviewed for each case and the extent of endometriosis or adhesions or both were classified according to a system proposed by the American Fertility Society.[31] This classification system is a four-stage model (mild, moderate, severe and extensive) based on the site, size and type of endometrial involvement. Of the cases, 12% had a clinical diagnosis of endometriosis before the index date.

From 1,905 patients who had laparoscopy for tubal ligation during the same time period, 200 fertile controls were chosen. Controls were matched to the cases by age (± 2 years) at the time of laparoscopy and by clinic registration numbers so that the length of time of medical care in the Mayo system was similar. The approach of comparing fertile and infertile populations for endometriosis as documented by laparoscopy was considered to be superior to previous reports relating endometriosis and infertility based on data describing conception after treatment of endometriosis. However, several caveats must be inserted. Both cases and controls were taken from the clinic referral series, and a bias in the choice of patients certainly exists. A population-based case-control study was not deemed feasible given the relatively small population of Rochester, Minnesota. Second, by the nature of the design, the comparison is extreme.

Of the infertile patients, 21/100 (21%) were found to have endometriosis, including 11 mild, 8 moderate and 2 severe cases. Among the 200 fertile controls, only 4 (2%) had evidence of endometriosis, all staged as mild. Thus, endometriosis is significantly more common ($\chi^2_1 = 31.52$, $P < .001$) and, when present, more severe in infertile as compared with fertile patient populations. These findings serve to confirm the clinical impression that an association between endometriosis and infertility exists, but casts little light on the direction of the causation. A question regarding this study is whether the fertile control population was capable of pregnancy because of the absence of endometriosis or whether there was an absence of endometriosis because of past pregnancies. One can look at two types of information to try and answer this question: the type of infertility present in patients with endometriosis and the relative frequency distributions of obstetric history before a laparoscopy.

In the Mayo study 16 of 21 patients (76%) had primary infertility, which is in close accord with Buttram's[21] work, in which 71% of 206 infertility patients had primary endometriosis. One could argue that when endometriosis is present, it is

more likely that the patient has never been pregnant. However, Kistner[32] has suggested that infertile women, particularly those with endometriosis, have more fetal losses than do normal women. Data from the Mayo study do not support this: infertile nonendometriosis cases showed a rate of fetal loss three times that of infertile endometriosis cases; both infertile groups combined indicated less fetal loss than normal controls (21% to 24%). Although speculative, it would seem that a tendency does exist for patients with endometriosis never to have been pregnant (Table 1). The prevalence of endometriosis in this study (21%) agrees in general with other reports of the frequency of endometriosis diagnosed by laparoscopy in populations treated primarily for infertility rather than for pain or mass (5% to 30%).[11] Also, the distribution of endometriosis in this case-control study was skewed to less severe or extensive involvement (stages 1 and 2).

TABLE 1.—*Frequency of Obstetric Events Before the Index Date Among 100 Women Evaluated for Infertility and 200 Matched Control Subjects Undergoing Tubal Ligation**

Obstetric Event	Group	% Frequency By No. of Occurrences 0	1	2	≥3
Pregnancy	Case	60	25	5	10
	Control	. . .	10	44.5	45.5
Birth	Case	70	24	5	1
	Control	. . .	12.5	54	33.5
Intrauterine death	Case	79	16	1	4
	Control	76	16	5	3
Ectopic pregnancy	Case	98	1	1	. . .
	Control	99.5	0.5	. . .	. . .
Spontaneous abortion†	Case	84	12	. . .	4
	Control	82.5	12.5	3	2
Induced abortion	Case	97	3	. . .	. . .
	Control	95.5	3.5	0.5	0.5
Stillbirth‡	Case	100	. . .	. . .	. . .
	Control	95.5	4.5	. . .	. . .

*From Strathy et al.[29]
†Gestation ≤20 weeks or fetus <500 grams.
‡Gestation ≥20 weeks or fetus >500 grams.

Demographic Considerations

At least part of the suggested increase in the incidence of endometriosis can be attributed to the relative availability of laparoscopy for the diagnosis of pelvic conditions in recent years. This can also account for the comparatively low occurrence in certain racial and socioeconomic groups, with the less affluent being constrained in their access to and utilization of medical resources for the complete investigation of pain or infertility or both.

Another portion of the suggested increase in endometriosis can be attributed to changes in the demographic pattern of fertility in some western nations during the past few decades. Specifically, given that pregnancy protects against endometriosis, a pattern of lower parity and delayed pregnancy could result in increased occurrence of the disease. The national trend to delay childbearing is reflected in a reported 37% increase between 1975 and 1979 in the number of women in the United States who had their first child between ages 30 and 35 years.[33] In general, as ages at first marriage and first birth increase, rapid fertility decreases as measured by the proportion having a birth within a given period after marriage or a preceding birth.[34,35] In turn, there is a tendency for women with a long first-birth interval to have a long second-birth interval as well.[36] Coupled with the limited reproductive span and the widespread availability of organized family planning programs, these factors have served to lower the parity profile in many western countries. For a parity-related disease, such as endometriosis, these factors could induce an increase in incidence through time by increasing the period when women of reproductive age are at risk.

A second major fertility variable that could affect the occurrence of endometriosis is a change in the age at menarche. Of the various factors that may account for rising preteen and early teen sexuality, pregnancy and fertility, one of the most commonly cited is a drop in the age of menarche. Specifically, the average age at menarche for United States resident women was thought to have dropped from 17 years in the 19th century to 12.5 years today.[37] If the proposed drop in age at menarche is true, the length of the reproductive span would increase. Given the nature of endometriosis, this could result in an increased occurrence. However, Bullough[38] has argued that while there has been some drop in the age at menarche in the United States over the past century, it has been less than assumed, with the 17-year average age at menarche for the 19th century being a misinterpretation of historical data. The more accurate age for the 19th century is estimated to be between 12 and 14 years, although some sources continue to set a later date.[5] If Bullough's interpretation is followed, the drop in average age at menarche for the United States populations over the past century has been, at most, less than two years. Spread over a century, it is unlikely that such a drop could account for any real increase in the frequency of endometriosis.

Summary and Recommendations

At least three factors could contribute to a purported rise in endometriosis. The first is the increased use of laparoscopy as a diagnostic technique during the past few decades. The real incidence of the disease would not be increasing, but more of it is being found. The second and third factors, lower parity and delayed pregnancy, could be causing an actual increase in disease occurrence.

There is a clinical consensus on the association of endometriosis and infertility, but little consensus on the direction of the causation or on the etiology of endometriosis itself. The epidemiology of endometriosis is severely limited by the difficulty of the diagnosis, and this is unlikely to improve substantially. It is necessary to use surgical incidence studies as the main source of epidemiologic data, and such records have inherent limitations of referral and sample selection bias.

Three epidemiologic tools could be used to further our knowledge of endometriosis. Additional case-control studies could be carried out in other medical institutions to further evaluate the association with infertility. Because the Mayo Clinic study population was 99% white, case-control studies based on other racial groups and socioeconomic strata would be of comparative value. The notion of an endometriosis personality type should be further investigated. Although establishing correlations of psychologic traits with susceptibility to the development of disease is difficult, if recurring patterns have been observed by clinicians, they should be documented

by appropriate sociologic, physical and psychological measures. A pilot questionnaire to clinicians working with endometriosis patients would be a simple first step. Third, life-table analysis could be carried out in a prospective manner on the results of the therapy for infertility among endometriosis patients. A notable application of the life-table method to the study of endometriosis is the report by Adamson and co-workers.[39] If coupled with a relatively homogeneous patient population and the classification system for endometriosis of the American Fertility Society, such a method of presenting treatment results would aid in the comparative evaluation of regimens and allow patient and physician to evaluate together the statistical childbearing expectancies of various therapies. It might also lend itself to evaluating biologically plausible explanations for the conundrum of mild endometriosis and infertility.

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Intestinal Parasites in Southeast Asian Refugee Children

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To determine the predictability of pediatric stool-parasite patterns among various Southeast Asian ethnic groups, I collected data from medical and microbiology laboratory records on all Southeast Asian refugee children who had a stool specimen examined for ova and parasites over a 21-month period. For most of the children, the specimen was examined as part of routine "health screening." The patterns of infection by ethnic group for those Vietnamese and Laotian children living in Seattle differ from the patterns seen in other geographic areas.

(Parish RA: Intestinal parasites in Southeast Asian refugee children. West J Med 1985 Jul; 143:47-49)

Of the many studies in which the infection rates and varieties of intestinal parasites in Southeast Asian refugees now living in the United States have been examined, only two focused specifically on children.[1,2] In the study by Tittle and co-workers, 65 out of 100 Southeast Asian pediatric patients had one or more intestinal parasites present on initial screening ova and parasite examination.[2] These authors also suggested that different patterns of stool parasites occur among different ethnic groups within the Southeast Asian pediatric refugee population.

I did a retrospective study to examine a larger series of Southeast Asian children with intestinal parasites and to determine whether the notion of discrete stool-parasite patterns among various ethnic groups is valid in the Seattle area.

Patients and Methods

Data were collected from the medical records and Microbiology Laboratory records of all Southeast Asian children whose stool specimens were examined for ova and parasites between March 1, 1981, and December 31, 1982, a time of maximum refugee influx to the Seattle area. All had been in the United States for fewer than 18 months at the time of initial visit and presented to the Harborview Medical Center Pediatric Clinic for initial health screening and ongoing well-child care. Stool specimens were examined for ova and parasites as part of well-child care and health screening in 75% of the children, who were asymptomatic; in the remaining 25%, the stool specimens were examined for ova and parasites as part of an evaluation for abdominal pain, diarrhea or failure to thrive (or all of these).

Stool specimens were examined for parasites by one of three laboratory technicians in the Microbiology Laboratory at Harborview Medical Center. Fresh specimens were preserved in polyvinyl alcohol and 10% formaldehyde solution at a ratio of approximately one part stool to four parts preservative; these were processed by direct-formaldehyde solution-ether concentration of formalinized material and Wheatley trichrome stain of polyvinyl alcohol material.[3]

Results

The total number of stool ova and parasite specimens submitted from Southeast Asian children seen in Pediatric Clinic during the 21-month period was 461. Of these 461 specimens, 338 represented a child's first specimen examined, and these 338 children became the study population. Of those patients, 184 were Laotian (lowland), 5 were Lao-Mien, 14 were Hmong, 102 were Khmer (Cambodian) and 33 were Vietnamese. Ages ranged from 5 weeks to 16 years, with a mean age of 6.5 years. There were no significant differences in age distribution, sex or time of US arrival among the ethnic groups.

Table 1 lists the number of positive identifications and the distribution of multiple infections among the 338 patients. Roughly half of those examined had one or more parasites identified (positivity rate, 55.6%), and of those with positive findings, half had multiple species identified. In our sample, no child younger than 6 months had an intestinal parasite found in a stool specimen.

Table 2 shows the number of children in each ethnic group with one or more positive identification(s) and the total number of parasite species positively identified for all children in that ethnic cohort. The Laotian children appear to

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have a slightly higher average number of different parasites per infected child than other ethnic groups. The cohorts differed significantly in their positivity rates ($\chi^2=19.61$, degrees of freedom [df]=4, $P<.001$). Partitioning of the groups[4] indicated that Laotians and Cambodians as a group had significantly greater positivity rates than did the Lao-Mien, Hmong and Vietnamese as a group.

Table 3 gives the positive identifications by species of parasite and the ethnic origin of the children. The parasite species are arranged in decreasing frequency of identification for the whole sample. The first three species (*Giardia lamblia*, hookworm and *Clonorchis sinensis*) accounted for 56.2% of all positive identifications. *G lamblia*, *C sinensis*, *Trichuris trichiura* and *Hymenolepis nana* all showed significant differences in infection rates across the three ethnic groups that resulted when the Lao-Mien and Hmong children were combined into a single cohort with the lowland Laotian children.

TABLE 1.—*Children in Sample (N=338) With Single and Multiple Parasites Identified in Stool**

Parasites	Children With Pos. Specimen — Number	Parasites Identified — Number	
Single	94	(×1)	94
2	57	(×2)	114
3	22	(×3)	66
4	13	(×4)	52
5	1	(×5)	5
6	1	(×6)	6
Total	188		337

*Overall positivity rate=55.6 per 100 specimens.

Discussion

The positivity rate for parasite infection found by examining a single stool specimen in this pediatric population (55.6%) is comparable to the rate seen in adult populations

TABLE 2.—*Children Tested and Positive Identifications by Ethnic Group**

Ethnic Group	Children Tested — Number	Children With Pos. Stools for Parasites — Number	Organisms Identified — Number	Parasites per Infected Child — Mean	Positivity Rate† — Percent
Laotian	184	107	205	1.92	58.2
Lao-Mien	5	2	3	1.50	40.0
Khmer (Cambodian)	102	66	110	1.67	64.7
Hmong	14	3	5	1.67	21.4
Vietnamese	33	10	14	1.40	30.3
Totals	338	188	337	1.79‡	55.6‡

*Test of significance of differences between ethnic groups: $\chi^2=19.61$ (df=4), $P<.001$.
†Positivity rate equals percent of infected children among those tested.
‡Weighted mean.

TABLE 3.—*Number of Children in Each Ethnic Group Infested by Each Species of Parasite**

Organisms	Laotian — Number (Percent)	Lao-Mien — Number (Percent)	Hmong — Number (Percent)	Khmer (Cambodian) — Number (Percent)	Vietnamese — Number (Percent)	Total — Number (Percent)	Difference Among Ethnic Groups†
Giardia lamblia	45 (24.5)	2 (40.0)	0	24 (23.5)	1 (3.0)	72 (21.3)	$P<.05$
Hookworm	34 (18.5)	1 (20.0)	2 (14.3)	28 (27.4)	5 (15.1)	70 (20.7)	NS
Clonorchis sinensis	44 (23.9)	0	0	2 (2.0)	2 (6.1)	48 (14.2)	$P<.001$
Strongyloides stercoralis	15 (8.1)	0	0	15 (14.7)	1 (3.0)	31 (9.2)	NS
Endolimax nana	13 (7.1)	0	1 (7.1)	14 (13.7)	2 (6.1)	30 (8.9)	NS
Trichuris trichiura	20 (10.9)	0	2 (14.3)	2 (2.0)	3 (9.1)	27 (8.0)	$P<.05$
Entamoeba coli	16 (8.7)	0	1 (7.1)	6 (5.9)	0	23 (6.8)	NS
Hymenolepis nana	5 (2.7)	0	0	11 (10.8)	0	16 (4.7)	$P<.005$
Ascaris lumbricoides	5 (2.7)	0	0	2 (2.0)	0	7 (2.1)	. . .
Entamoeba histolytica	2 (1.1)	0	0	2 (2.0)	0	4 (1.2)	. . .
Entamoeba hartmanni	1 (0.5)	0	0	2 (2.0)	0	3 (0.9)	. . .
Iodamoeba bütschlii	2 (1.1)	0	0	0	0	2 (0.6)	. . .
Trichomonas hominis	1 (0.5)	0	0	1 (1.0)	0	2 (0.6)	. . .
Entamoeba polecki	0	0	0	1 (1.0)	0	1 (0.3)	. . .
Taenia species	1 (0.5)	0	0	0	0	1 (0.3)	. . .
Total Positive Identifications	204	3	6	110	14	337	
Total Number of Children Tested	184	5	14	102	33	338	

NS=no significance

*Numbers in parentheses represent percentage of children in that ethnic group who were examined and found to have the parasite.
†For purposes of evaluating differences among ethnic groups, the Laotian, Lao-Mien and Hmong children were aggregated into a single group. Differences were tested with χ^2, $df=2$.

studied.[5-11] *G lamblia* and hookworm are the most frequently encountered of the intestinal parasites in our Southeast Asian pediatric population, followed closely by *Clonorchis, Strongyloides stercoralis* and *Endolimax nana.* No clear predominance of nematodes, cestodes, trematodes or protozoa appeared in this population.

Our patterns of organism prevalence by ethnic origin differ from those found in other pediatric studies, which also reported findings on a single stool specimen. Goldsmith and associates found *Giardia, Ascaris* and *Entamoeba histolytica* the most common intestinal parasites among Vietnamese infants in San Francisco,[1] although this study looked only at children younger than 1 year. In our Vietnamese group, hookworm and *Trichuris* were most common. Tittle and colleagues found that Laotian children, ages 2 weeks to 17 years (N=36) had hookworm and *Trichuris,*[2] whereas in our sample *Giardia* and *Clonorchis* were most frequent. (In fact, 94% of all *Clonorchis* found was identified among lowland Laotians.) Cambodian children in Tittle's and our study had predominantly hookworm, *Giardia* and *Strongyloides.* The number of children in our sample from the smaller ethnic groups (Lao-Mien, 5; Hmong, 15) was too small to evaluate statistical significance.

Other studies looking at various Indochinese refugee populations of all ages have indicated that people of different ethnic origins will have different intestinal parasites.[12-15] However, most of the reports on Southeast Asian refugees have not separated ethnic groups, but have "lumped" all Southeast Asian refugees together.[5-11]

Of the intestinal parasites found in our pediatric population, *Entamoeba coli, Endolimax nana, Iodamoeba bütschlii* and *Entamoeba hartmanni* are considered nonpathogenic and do not need treatment. Effective therapies are available for the other parasitic infections, however, as has recently been reported in an excellent review.[16]

Summary

The patterns of parasite infection by ethnic group in the Seattle child-refugee population may not be identical with those found elsewhere. Routine screening of asymptomatic patients in pediatric refugee populations for the presence of intestinal parasites appears to be warranted in the Seattle area.

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Nonoperative Management of Acute Idiopathic Colonic Pseudo-Obstruction (Ogilvie's Syndrome)

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In a four-year experience (35 episodes in 27 patients) with the use of medical and colonoscopic therapy for acute idiopathic colonic pseudo-obstruction, we have found that initial conservative measures followed by flexible colonoscopy in nonresponders are effective and safe. Contrary to previous reports, an initial nonoperative approach including colonoscopy is frequently successful and the outcome with this approach is not adversely affected even in the few patients who eventually require surgical decompression.

(Fausel CS, Goff JS: Nonoperative management of acute idiopathic colonic pseudo-obstruction [Ogilvie's syndrome]. West J Med 1985 Jul; 143:50-54)

Acute colonic pseudo-obstruction, first described in 1948 by Ogilvie,[1] is a nonmechanical dilatation of the colon often associated with severe illness or injury. Synonyms for the condition include Ogilvie's syndrome, colonic ileus, large intestinal colic and idiopathic large bowel obstruction. The dilatation involves the cecum and varying lengths of more distal colon. Often a "cutoff" of distention can be identified at the hepatic, splenic or sigmoid flexures. Cecal distention may become extreme (up to 20 cm or more) and result in perforation.

Because patients with acute colonic pseudo-obstruction usually are very ill, noninvasive treatment often is attempted in hopes of avoiding surgical intervention. However, cecal perforation is an understandably feared risk of such a conservative approach, so there are many proponents of emergency operation. This dilemma is intensified by inconsistencies in indications given for operation. There is no agreement on the maximal permissible distention of the cecum, and some[2-4] have advocated doing a surgical procedure immediately, whereas others[5,6] prefer a trial of conservative therapy first. In addition, it is important to differentiate true colonic obstruction from pseudo-obstruction although guidelines for surgical intervention in cases of true obstruction are also not well defined. A water-soluble contrast barium enema is probably the quickest and safest way to distinguish between true obstruction and pseudo-obstruction, though this can also be accomplished with colonoscopy.

As an alternative to operative decompression, Kukora and Dent[7] used colonoscopy with a flexible instrument. Since that small series (five patients) was reported in 1977, other reports have appeared, but only two are larger.[8,9]

In an effort to more precisely define the clinical course of acute colonic pseudo-obstruction and the response to and indications for various kinds of therapy (colonoscopic decompression in particular), we have reviewed our experience of four years.

Patients and Methods

We have reviewed the courses of all patients referred to the Gastroenterology Service with possible acute colonic pseudo-obstruction and those of all other patients with that diagnosis in our institutions (University of Colorado Hospital and Denver Veterans Administration Medical Center [VAMC] from January 1, 1979, through December 31, 1982. Acute colonic pseudo-obstruction was diagnosed if the cecum was acutely dilated to more than 9 cm with or without varying degrees of small bowel dilatation on plain roentgenograms of the abdomen. Cases of true mechanical obstruction (luminal compromise by intrinsic lesions or by extrinsic compression) or toxic megacolon (colonic dilatation due to inflammatory disease) were excluded in all patients either by colonoscopic examination, contrast radiography or by clinical presentation and subsequent course. No patients had the syndrome of chronic idiopathic intestinal pseudo-obstruction.

Retrospectively, three levels of treatment were defined: level 1—nasogastric suction, rectal tube, enemas, correcting electrolyte disturbances and withdrawing narcotic therapy; level 2—level 1 plus colonoscopic decompression; level 3—operative decompression.

All patients were treated with some level 1 modalities (see Table 1) for varying periods of time before referral to the Gastroenterology Service. Patients in whom the cecal diam-

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TABLE 1.—*Patient Profile, Management and Outcome in 27 Patients (35 Episodes) With Acute Ogilvie's Syndrome*

Patient	Age (yr), Sex	Maximal Cecal Diameter (cm)	Diagnoses	Therapy						Cecal Size After Colonoscopy (cm)	Outcome
				Narcotic Treatment	Nasogastric Tube	Rectal Tube	Enemas	Colonoscopy	Surgery		
1	68 ♂	13	Retroperitoneal hematoma, renal failure	Yes	Yes	Yes	Sodium phosphate-biphosphate (Fleet's Phospho-Soda)	No	No		Resolved in 3 days
2	23 ♀	13	Cesarean section	Yes	Yes	Yes	No	No	No		Resolved in 2 days
3	75 ♂	14	Prostate cancer	Yes	Yes	Yes	Soap suds ×3	No	Cecostomy		Resolved
4	48 ♂	13	Multiple sclerosis	Yes	Yes	Yes	Fleet's ×2	No	No		Resolved
4*	48 ♂	11	Recurrence in 2 days	No	Yes	Yes	Tap water	No	No		Resolved
5	60 ♀	9.5	Hip fracture	Yes	Yes	No	No	No	No		Resolved
6	62 ♀	14	Diabetic ketoacidosis, hypocalcemia	No	Yes	No	No	No	No		Resolved
7	60 ♀	14	Cerebellar tumor	Yes	Yes	Yes	Meglumine diatrizoate (Gastrografin)	No	No		Resolved in 2 days
8	70 ♂	11	Appendectomy, myocardial infarction	Yes	Yes	Yes	No	No	No		Resolved in 3 days
9	60 ♂	12	Colchicine toxicity	No	Yes	No	No	Refused	No		Resolved in 5 days
10	78 ♀	11	Hip fracture	Yes	Yes	No	No	No	No		Resolved in 2 days
11	67 ♀	17	Lung cancer, mechanical ventilation	No	Yes	No	No	Not offered	Not offered		Perforation, death
12	56 ♂	12	Leg fracture	Yes	Yes	Yes	No	No	No		Improved
12*	56 ♂	14	Recurrence in 3 days	No	Yes	Yes	No	Yes	No	9	Resolved
13	46 ♀	15	Hysterectomy, retro-peritoneal hematoma	No	Yes	No	No	Yes	No		Resolved
14	61 ♂	12	Metastatic cancer	Yes	Yes	No	No	Yes	No		Resolved, died of cancer
15	64 ♂	12	Renal failure, mechanical ventilation	Yes	Yes	Yes	No	No	No		Improved
15*	64 ♂	12	Recurrence in 2 days	No	No	No	No	Yes	No		Resolved
16	68 ♂	12	Leg fracture	Yes	Yes	Yes	Tap water	Yes	No		Resolved
17	67 ♂	12	Leukemia, prostate operation	No	Yes	Yes	No	Yes	Laparotomy		Colonoscopy failed, ischemic small bowel
18	69 ♂	14	Lymphoma, mechanical ventilation	Yes	Yes	No	No	Yes	No		Resolved, died of sepsis
19	60 ♂	12	Hip fracture	Yes	Yes	No	No	Yes	No	9	Improved
19*	60 ♂	13	Recurrence in 1 day	No	Yes	No	No	Yes	No	9	Improved
19*	60 ♂	12	Recurrence in 1 day	No	Yes	No	No	No	Cecostomy		Resolved
20	63 ♂	12	Hypokalemia, hyponatremia	Yes	Yes	Yes	No	Yes	No	8	Resolved
21	73 ♂	12	Lung cancer, sepsis	No	Yes	Yes	Tap water, Fleet's ×4	Yes	No		Resolved
22	61 ♀	14	Metastatic cancer	Yes	Yes	Yes	No	Yes	No	7	Resolved
23	78 ♂	14	Renal failure, mechanical ventilation	Yes	Yes	No	No	Yes	No	10	Improved
23*	78 ♂	13	Recurrence in 2 days	No	Yes	No	No	Yes	No	6	Resolved, died of renal failure
24	67 ♂	15	Leukemia, sepsis, mechanical ventilation, hyponatremia	No	Yes	No	No	Yes	No	8	Resolved, died of sepsis
25	57 ♂	15	Renal failure, mechanical ventilation	No	Yes	No	No	Yes	No	8	Resolved, died of renal failure
26	80 ♂	12	Leg fracture, renal failure	Yes	Yes	Yes	No	Yes	No	9	Improved
26*	80 ♂	12	Recurrence in 1 day	No	Yes	No	No	Yes	Cecostomy		Colonoscopy failed, died of renal failure
27	76 ♂	12	Stroke, sepsis, mechanical ventilation, renal failure	No	Yes	Yes	No	No	Laparotomy		No abnormalities at operation
27*	76 ♂	12	Recurrence in 1 day	Yes	Yes	No	No	Yes	No	9	Resolved, died of renal failure

*Same patient with recurrence.

eter equaled or exceeded 12 cm despite level 1 measures were deemed treatment failures and immediately had colonoscopic decompression with an Olympus TCF-2L flexible colonoscope. No specific bowel preparation preceded the procedure. An attempt was made to insufflate the smallest amount of air possible to visualize the lumen in the distal colon. When the ascending colon was reached, the colonoscope was slowly withdrawn while keeping the scope in the center of the lumen and using suction to remove the air and fluid contents. Colonoscopic success was defined as a decrease in the abdominal distention and a decrease in cecal diameter of more than 3 cm, as documented by a postprocedure plain roentgenogram of the abdomen. Eight cases (patients 1 to 8 in Table 1) were not referred to the Gastroenterology Service but were found by chart review. Review of these cases was felt to be important so as to better assess the natural history of conservatively treated acute colonic pseudo-obstruction uninterrupted by colonoscopic intervention at a predetermined cecal diameter.

Results

Patient Profile

There were 27 patients—20 men and 7 women—with 35 individual episodes of acute colonic pseudo-obstruction. The male predominance probably reflects the fact that most of the patients were seen at the Denver VAMC. Patients' ages ranged from 23 to 80 years (mean, 61 years). All patients had severe associated illnesses including cancer (nine), metabolic abnormalities (seven), respiratory failure requiring mechanical ventilation (seven), nongastrointestinal infections (eight), fractures (six) and drug toxicity (four).

Symptoms, Signs and Laboratory Tests

The most common presenting symptom of acute colonic pseudo-obstruction was abdominal distention. The rapidity of onset of distention was variable, but no patient had a fulminant course (a few hours from onset to perforation) or perforation unaccompanied by recognized distention. Most patients had mild to moderate discomfort, but a few complained of more severe, crampy abdominal pain; most had constipation, although a small number presented initially with watery stools and continued to pass small amounts of flatus. Some patients had nausea but none vomited.

Physical examination in all cases showed massive abdominal distention. Usually there was mild to moderate tenderness and peritoneal signs were rare in uncomplicated cases; in one patient with ischemic small bowel and in one with cecal perforation, severe abdominal tenderness and signs of diffuse peritoneal irritation subsequently developed. Bowel sounds were variably diminished, normal or high pitched. Fifteen patients (56%) had low-grade fever that appeared to be temporally correlated with the presence of acute colonic pseudo-obstruction rather than the associated illness.

Laboratory tests were not helpful in making the diagnosis, although metabolic abnormalities often were present. Leukocytosis was frequently present but was not specific for acute colonic pseudo-obstruction.

Radiographic Studies

In all cases, the diagnosis was suggested by the finding of colonic distention on radiologic examination of the abdomen (Figure 1). Cecal diameters ranged from 9 to 17 cm, with the majority (26 cases) measuring from 12 to 14 cm. Other diagnoses considered in all cases included true colonic obstruction, ischemic colitis and toxic megacolon. Free intraperitoneal air was not found on any initial film and was detected only once on subsequent examination in a patient with terminal metastatic carcinoma whose initial cecal diameter was 17 cm (patient 11). Many patients had a relative "cutoff" of colonic air at the hepatic, splenic or sigmoid flexures, although some distal air was almost always present.

Outcome of Therapy

All 35 episodes were initially managed for variable periods with level 1 treatment. Twelve episodes responded to level 1 treatment but there were three recurrences (see Table 1). One recurrence was successfully managed with level 1 treatment while the other two were treated successfully with colonoscopy (level 2). One other patient received level 1 therapy that was unsuccessful. This patient's cecum measured 17 cm at diagnosis and eventually perforated. No level 2 or 3 therapy was attempted because of the patient's terminal state from lung cancer.

Nine patients were successfully treated with colonoscopy when their cecal diameters equaled or exceeded 12 cm and had not responded to level 1 therapy during the first episode. In three patients colonoscopy was initially successful but recurrences developed. One patient (23) had a permanent resolution after a second colonoscopic decompression. Patient 26 had a second colonoscopy that was unsuccessful because of a large amount of sigmoid feces. During surgical intervention, splitting of the teniae coli was noted and a cecostomy was done. The third patient (19) had a second successful decompression, but was taken to surgery after a third recurrence one day later. During the operation, he was found to have splitting of the teniae coli and a localized area of necrosis with perforation of the cecum. A cecostomy was successfully carried out. One colonoscopic decompression was done after patient 27 had a recurrence one day after a laparotomy for cecal dilatation (no cecostomy was done). The colon remained decompressed after the colonscopy until the patient died many days later of renal failure.

We found that gross decompression of abdominal distention could not be achieved until the colonoscope was passed beyond the hepatic flexure. Once the cecum was reached, a visible decrease in the abdominal girth would occur quickly when suction was applied through the colonoscope.

Five patients eventually had a cecostomy, all of which were considered successful in achieving colonic decompression. One was carried out in a patient (19) in whom colonoscopic decompression was initially successful but who had a recurrence. Two were done after unsuccessful attempts at decompression (one in a patient [26] with a recurrence) and the other two were performed after a brief attempt at level 1 therapy without considering colonoscopy.

There were no complications from the 19 colonoscopies. Only one patient (11) died in whom colonic pseudo-obstruction was considered a major contributing factor. The overall mortality rate from all causes in the series was 30%.

Discussion

Acute colonic pseudo-obstruction has been considered a rare syndrome, but we found 27 patients with this condition in

four years at our two institutions. The condition also has been considered life-threatening, often requiring surgical intervention. In our experience, though, initial conservative therapy seemed to be effective or was unassociated with an adverse outcome. Moreover, the mortality rate attributable to pseudo-obstruction per se was low.

The major concern in acute colonic pseudo-obstruction is cecal perforation, but this concern must be balanced by the high risk of cecostomy in an ill patient with an unprepared bowel. This risk naturally has led to considering colonoscopic decompression as an alternative form of treatment. From our experience with colonoscopy in this series, we conclude the following:

- Colonoscopic decompression can be accomplished in

Figure 1.—Representative abdominal roentgenograms of two patients before (**A** and **C**) and immediately after (**B** and **D**) successful colonoscopic decompression.

most cases of acute idiopathic colonic pseudo-obstruction with only moderate difficulty despite no cleansing of the colon.

- The procedure, if carefully carried out, is not hazardous.
- Contrary to other reports,[8,9] effective decompression of the colon often required passage of the colonoscope into the ascending colon.
- The use of colonoscopy may avoid an operation in patients with massively dilated cecums and thus reduce the mortality rate.
- In addition to achieving colonic decompression, full colonoscopy can make a diagnosis of acute colonic pseudo-obstruction definitive by excluding true obstructing lesions or mucosal lesions such as ischemia.

The issue of the maximal size of the cecum that should be permitted before intervening with colonoscopy is difficult to resolve. Various authors have recommended some form of intervention when the cecum reaches 9 cm,[2,7,10,11] 10 cm[12] or 12 cm[3-5] in diameter, but the basis for these recommendations is arbitrary. Only 42 cases of perforation due to acute colonic pseudo-obstruction have been reported in the English language literature.[11] Only four reports actually record a cecal diameter before perforation (20 cm, 16 cm, 15 cm, 14 cm). Others have reported smaller cecal size at the time of the diagnosis of perforation. Because perforation can effect significant decompression, we doubt the applicability of reports of cecal size measured at the time perforation is diagnosed. Furthermore, we have found that most patients with typical, uncomplicated, acute colonic pseudo-obstruction can tolerate a cecal diameter of 14 cm, at least temporarily. Obviously, it is better not to allow this degree of colonic distention to develop or to persist for prolonged periods, as local perforation of the cecum occurred in one of our patients whose cecum had reached 12 cm in diameter.

It is unlikely that a randomized trial of various forms of treatment in cases of acute idiopathic colonic pseudo-obstruction will ever be done. Therefore, on the basis of our experience, we make the following recommendations for treatment of this condition: A trial of conservative measures—nasogastric suction, rectal tube, correction of metabolic abnormalities or discontinuation of medications that might interfere with bowel motility—is in order initially. If this approach is unsuccessful as assessed by abdominal films every 6 to 12 hours that show an increasing cecal diameter, or if the cecal diameter has reached 12 cm or more at the time of diagnosis, colonoscopy to decompress the colon should be done. Colonoscopy may have to be repeated in a select number of cases. A cecostomy should be done only if signs of possible perforation of the cecum—high fever, severe abdominal tenderness, referred rebound tenderness or loss of liver dullness—are present before colonoscopy can be done or if conservative therapy and colonoscopy are unsuccessful.

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Anaphylactoid Reactions to Tolmetin After Interrupted Dosage

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Seven patients had anaphylactoid reactions after ingesting tolmetin sodium. In each case the reaction followed readministration of the drug after an interrupted period of at least three days and within 90 minutes of taking a single 400-mg capsule. None of the patients had had prior anaphylaxis and none were judged atopic. Skin tests to an extract of the drug (0.02 mg) were uniformly negative, whereas a higher concentration produced a nonspecific irritant reaction. In vitro tests in one patient for IgE antibodies to tolmetin and for complement activation were negative.

(Bretza JA, Novey HS: Anaphylactoid reactions to tolmetin after interrupted dosage. West J Med 1985 Jul; 143:55-59)

Anaphylactoid reactions to tolmetin sodium (Tolectin) is a recently described phenomenon that may have a higher incidence than that for other nonsteroidal anti-inflammatory drugs (NSAIDs).[1-7] Pertinent in the tolmetin-sensitive patients is that they do not have asthma or chronic urticaria. In addition, these persons previously ingested the drug with impunity but, after stopping the drug therapy for various lengths of time, had an immediate hypersensitivity reaction on first readministration. In the following report we describe seven cases of "second exposure" tolmetin reactions. One patient in whom respiratory difficulty developed with the use of tolmetin underwent an aspirin challenge test to determine whether his anaphylactoid reaction was generalized to other cyclooxygenase inhibitors. To gain insight into the pathogenesis of the reactions, selected in vivo and in vitro immunologic tests for immediate-type reactions were done.

Reports of Cases

Case 1

In August 1981, a 26-year-old student, a man with ankylosing spondylitis, ingested one 400-mg capsule of tolmetin and within 15 minutes had shortness of breath, coughing and wheezing, generalized pruritus and swelling about the lips and eyes. The patient "passed out" on the kitchen floor. He was put to bed by his wife and declined emergency treatment after recovery from the syncope. On examination in the clinic the following day, there were mild periorbital and lip swelling and generalized erythroderma. The lungs were clear to auscultation. Laboratory studies showed a hematocrit of 42% and a leukocyte count of 6,700 per μl without eosinophilia. His symptoms abated completely within 24 hours with no treatment. He had taken the medication without a day's interruption for more than two years until an episode of alcohol-induced gastritis prevented dosage the preceding four days.

A regimen of a non-prostaglandin-inhibiting drug, salsalate (Disalcid) was started that failed to relieve the patient's symptoms despite a blood salicylate concentration of 19 mg per dl. Because of his continued pain, the patient underwent an aspirin challenge test to find a safe substitute for tolmetin (see Methods and Materials and Results).

Case 2

The patient, a 52-year-old male engineer with sciatica, used tolmetin, 400-mg capsules, on a regular basis from December 1980 to May 1981. Following two epidural blocks in May 1981, he was almost painfree until November 1981. During this interval the patient took no medications. Following some lifting at work on November 4, 1981, he began to have a flare-up of his L-5 radiculopathy. Within 30 minutes of ingesting one 400-mg capsule of tolmetin, the patient had scattered welts, generalized itching and a "hot skin" sensation. He did not seek medical attention and his symptoms resolved within 24 hours. He was placed on a regimen of naproxen (Naprosyn) and had no reactions. Complete blood counts, including an eosinophil count, on specimens taken while he was on tolmetin therapy and three days after the tolmetin reaction disclosed no abnormalities.

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ABBREVIATIONS USED IN TEXT

NSAID = nonsteroidal anti-inflammatory drug
RAST = radioallergosorbent test

Case 3

A 56-year-old male executive with gout used tolmetin on a regular basis until he had a remission of symptoms in April 1981. From April 1981 through January 9, 1982, he took no medications. Podagra developed and he took one 400-mg capsule of tolmetin. Within 60 minutes he had generalized itching and intense burning of his skin. Accompanying this was a generalized scarlatinalike eruption. The patient commented that it felt like "my skin was intensely sunburned." His symptoms resolved the next day without treatment. He presently uses ibuprofen without difficulty. The patient had no history of drug allergy, atopy or eosinophilia.

Case 4

The patient, a 51-year-old housewife with rheumatoid arthritis, had used tolmetin continuously since April 1981. In March 1983, she had an upper respiratory tract infection and stopped taking tolmetin for three days. She resumed the tolmetin therapy and a diffuse itching and erythematous skin eruption developed within 45 minutes of ingesting the first capsule. By 18 hours the patient noticed a diffuse maculopapular rash. Her symptoms resolved with administration of diphenhydramine hydrochloride and avoiding futher use of tolmetin. She is able to use ibuprofen without reaction. The patient had no history of adverse reaction to drugs and eosinophilia was absent in blood specimens taken during tolmetin therapy.

Case 5

A 39-year-old housewife with sciatica had used tolmetin, 1,200 mg a day, on a regular basis from March until June 1982, when she stopped because of a remission. In January 1983, she ingested one 400-mg capsule of tolmetin because of an acute exacerbation of her radiculopathy. Within 30 minutes generalized erythroderma, pruritus and dizziness developed, which gradually abated by 24 hours without treatment except bed rest. She uses aspirin and ibuprofen without untoward reactions. The patient has no history of allergies or eosinophilia.

Case 6

This man, a 59-year-old pharmacy technician with osteoarthritis, had taken tolmetin regularly for six weeks. Following cessation of tolmetin therapy, he was treated with a one-week course of naproxen, 250 mg three times a day. When naproxen therapy did not provide relief, his physician prescribed indomethacin, 100 mg daily for a week. While on a two-week vacation he used no medications, but on returning to work he had an exacerbation of his osteoarthritis and ingested one 400-mg tolmetin capsule. Within 20 minutes the patient had intense pruritus of his scalp, chest congestion, respiratory stridor and generalized skin erythema with hives.

The patient was taken to an emergency room where he was treated with 3 liters per minute of oxygen given nasally; diphenhydramine, 50 mg given intramuscularly, and epinephrine, 0.3 ml of a 1:10,000 dilution given intravenously. His symptoms abated after an hour.

Laboratory studies included diagnostic skin tests to a battery of 60 common allergens, which were negative by prick and intradermal techniques, confirming his lack of atopy. Complete blood counts both before and a week after the reaction showed no abnormalities. Blood specimens taken after the reaction were prepared for immunologic studies (see Methods and Materials).

Case 7

The patient, a 55-year-old male clerical worker with lumbar spondylosis, had chest tightness, wheezing and flushing 90 minutes after taking one 400-mg capsule of tolmetin. Before this he had not used the drug for at least six months. The chest tightness and wheezing subsided spontaneously after 20 minutes. Over the next 12 to 18 hours intense pruritus, a maculopapular rash and hives developed (Figure 1). He was treated with diphenhydramine, 50 mg three times a day, and prednisone, 60 mg initially, which was tapered over a one-week course. The patient's leukocyte count, C3, C4 and total hemolytic complement levels were normal.

The cases are summarized in Table 1.

Methods and Materials

Immunologic Tests

Diagnostic skin tests. The tolmetin skin test was prepared by dissolving 200 mg tolmetin sodium in 20 ml of a sterile albumin-saline diluent (Hollister-Stier Laboratories, Spo-

TABLE 1.—*Anaphylactoid Reactions to Tolmetin on Second Exposure*

Patient	Age (yr), Sex	Onset of Reaction (min)	Type of Reaction	Interval Since Prior Exposure	Medical Condition	Other NSAIDs Used Before Tolmetin
1	26 ♂	15	Wheezing, pruritus, hypotension, periorbital edema	4 d	Ankylosing spondylitis	Sulindac, mefenamic acid
2	56 ♂	60	Pruritus, erythroderma	10 mo	Sciatica	Ibuprofen, sulindac
3	56 ♂	30	Angioderma, generalized pruritus, erythroderma	7 mo	Gout, obesity	None
4	51 ♀	45	Maculopapular rash, erythroderma, pruritus	3 d	Rheumatoid arthritis, upper respiratory tract infection	None
5	39 ♀	30	Hives, erythroderma, pruritus	13 mo	Sciatica	Ibuprofen
6	59 ♂	20	Hives, erythema, wheezing and shock	2 wk	Osteoarthritis	Naproxen, indomethacin
7*	55 ♂	90	Wheezing, maculopapular rash, hives and fever	6 mo	Lumbar spondylosis, nephrolithiasis, upper respiratory tract infection	Sulindac, naproxen

NSAID=nonsteroidal anti-inflammatory drug

*Only concomitant drug therapy was in this patient who took allopurinol, 300 mg daily for 6 years. He was given allopurinol again, without reaction. All patients had previously ingested aspirin without adverse reactions.

kane, Wash). The capsule, without medication, was also studied and was provided by McNeil Pharmaceuticals in a pulverized form and prepared similarly in a 20 mg per ml solution.

Skin tests were done by both the prick and intradermal techniques in ten healthy volunteers who never used tolmetin and ten patients who used the medication without adverse reactions. The application of 0.2 mg equivalent of tolmetin but not capsule material produced an immediate burning and erythema in all persons. This reaction was considered an irritant one. Intradermal tests with a 1:10 dilution that injected about 0.02 mg tolmetin was nonreactive in all control subjects. All the tolmetin-sensitive patients were given a prick test of the concentrate and, if the findings were negative, were tested intradermally with 0.02 mg tolmetin and capsule material. If the capsule skin test was negative, the patients were administered the capsule orally.

Radioallergosorbent test (RAST). Conjugates were prepared with tolmetin (provided by James Dale, MD, McNeil Pharmaceuticals, Spring House, Pa), 50 mg dissolved in 5 ml of 0.1 mol per liter sodium bicarbonate and 0.4% phenol and incubated with 100 mg cyanogen bromide-activated microcrystalline cellulose directly, or coupled to human serum albumin, 500 mg in 50 μl of 0.1 mol per liter sodium bicarbonate, before incubating with the cellulose matrix. Specimens of serum, 0.1 ml each from patient number 6 and ten subjects not known to have encountered the drug who served as controls, were mixed with 0.5-ml suspensions of each of the two conjugates above and monitored in an automatic gamma counter for the ability to bind anti-IgE ^{125}I (Pharmacia Laboratories, Piscataway, NJ). A total serum IgE level was measured by the PRIST technique using the Phadebas kit (Pharmacia Laboratories).

Complement studies. A specimen of whole blood from the same patient (patient 6) was frozen and sent in that state by express mail to John G. Curd, MD, Department of Clinical Research, Scripps Clinic and Research Foundation, La Jolla, Calif, who generously carried out the following complement studies: serum levels of C1q, C1r, C1s, C2 through C9 inclusive, properdin factor B, C3b inactivation, β_1H, C1 inhibitor and activation of C4 by rocket immunoelectrophoresis for C4d and C4. The patient's specimens were obtained 48 hours after the anaphylactoid reaction for the complement studies and six weeks later for the IgE studies.

Aspirin Challenge Test

To ensure maximum patient safety, patient 1 was admitted to hospital for 48 hours. Informed consent was obtained. An aspirin challenge test was carried out in the morning in case a

Figure 1.—Photographs of patient's skin eruption about 18 hours after he ingested a single, 400-mg capsule of tolmetin (patient 7). There are both maculopapular and urticarial lesions present. Intense pruritus accompanied these eruptions.

TABLE 2.—*Negative Aspirin Challenge Test in Tolmetin Sodium-Sensitive Patient (Case 1)*

Amount of Drug	Cumulative Dose mg	Time	Pulse Rate beats/min	Blood Pressure mm/mercury	FEV_1 liters	% Predicted FEV_1*	Symptoms
Baseline	...	7:00 AM	74	122/84	4.3	90	None
Placebo	...	7:05 AM	70	118/78	4.2	82	None
Aspirin, 5.0 mg	5	8:00 AM	92	138/88	4.4	99	None
Aspirin, 50 mg	55	10:00 AM	80	136/94	4.5	110	None
Aspirin, 100 mg	155	12:00 NOON	88	120/86	4.3	90	None
Aspirin, 150 mg	305	2:00 PM	76	126/86	4.4	99	None
Aspirin, 325 mg	625	4:00 PM	84	118/88	4.3	90	None
Aspirin, 650 mg	1,275	6:00 PM	78	122/78	4.5	110	None

FEV_1=forced expiratory volume in 1 second.

*A positive challenge reaction is defined as naso-ocular symptoms associated with bronchoconstriction recorded by a fall in $FEV_1 \geq 25\%$ below baseline

delayed or severe reaction necessitated resuscitative personnel or equipment.

After a free-flowing intravenous line was placed, the patient was given incremental doses of aspirin (Table 2). Monitoring of the cardiovascular and pulmonary status was done as shown in Table 2.

Results

Immunologic Tests

Skin tests. The skin tests to tolmetin were negative in the tolmetin-sensitive persons at the nonirritant dose (0.02 mg applied intradermally). This lack of specific skin reactivity indicated that an IgE-mediated reaction was absent in the skin. The prick and intradermal capsule skin tests and capsule ingestion challenges were negative in the patients, thus excluding involvement of the orange-colored capsule in the anaphylactoid reactions.

RAST. For the two RAST assays, with and without binding to human serum albumin, the radioactive counts per five minutes for patient 6 were 1,027 and 1,797, respectively, and the mean counts for the ten control serum specimens were 1,433 and 966, respectively. A positive RAST is considered a count 2.5 times or greater than the mean of the controls. These results are indicative of a negative study or the absence of specific IgE antibodies to tolmetin in the serum. The total serum IgE level was 46 units per ml, within the normal range.

Complement studies. Results of 16 different assays were within the normal range. The C4d:C4 ratio was also normal. There was no evidence of complement activation.

Aspirin Challenge Test

The aspirin challenge test (Table 2) was negative in patient 1, thus showing a lack of cross-reactivity to another prostaglandin synthetase inhibitor. The patient was able to tolerate standard doses of a structurally unrelated anti-inflammatory drug (ibuprofen) without a reaction, as did five other patients who experienced adverse reactions to tolmetin.

Discussion

The reactions in each case arose shortly after ingesting a capsule of tolmetin in patients who previously used the drug safely but had interrupted dosage for from 3 days to 13 months. The reactions can be termed anaphylactoid even though only the skin appeared to be involved in four patients. The reactions were of the immediate type and so alarmed the patients that they needed no medical advice to stop further dosing with the drug. Three had life-threatening episodes but these cleared without evident sequelae.

The term "anaphylaxis" is usually reserved for immediate reactions of an immunologic basis and, whereas the reactions occurring after prior exposure suggest sensitization, we found no evidence of an allergic reaction after limited studies. Skin test reactions in the patients did not differ from those in the control subjects, and no IgE antibodies were found in serum by the RAST method. There was also no evidence of complement activation in the single patient studies. Moreover, if an IgE-mediated mechanism were present, one would expect evidence of atopy by personal or family history or by skin tests to common allergens in some of the reactors. Antibody to some tolmetin metabolites cannot be excluded by these tests, however. The ability of the patients to tolerate aspirin and other cyclooxygenase inhibitors following their tolmetin reactions places this group in a category apart from other patients, usually with underlying asthma, who cross-react with several members of this drug group.[8]

More established is the relationship between these reactors and those reported to react to zomepirac sodium. Both tolmetin and zomepirac are closely related chemically as pyrrole acetic acid derivatives. They differ only by one methyl and one chlorine atom (Figure 2). Zomepirac was withdrawn

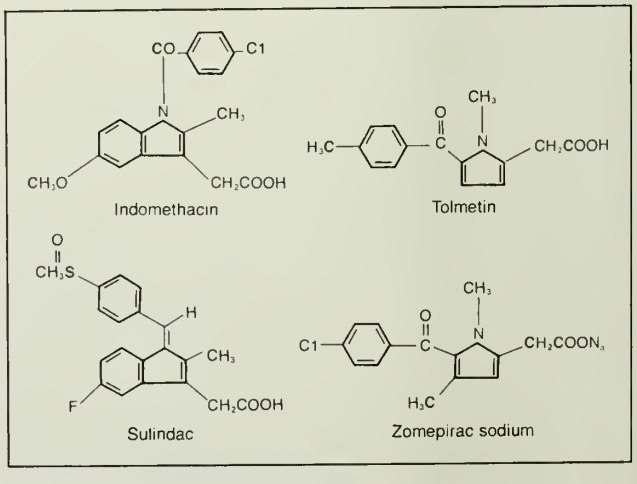

Figure 2.—Acetic acid derivations of nonsteroidal anti-inflammatory drugs. Indomethacin is an indole, sulindac is an indene derivative and tolmetin is a pyrrole analogue. Zomepirac, also a pyrrole acetic acid, resembles tolmetin both structurally and pharmacologically.

by its manufacturer on the basis of more than 1,000 suspected "allergic" reactions including five deaths, two in aspirin-sensitive patients.[9] There is a report of a case of consecutive anaphylactoid reactions to tolmetin and zomepirac in a patient who was able to subsequently tolerate aspirin.[5]

A report by officials of the Food and Drug Administration[1] noted what appeared to be an excessive number of anaphylactoid reactions to tolmetin. There is no ready explanation for the relatively large number of reactions from our two institutions. Neither rheumatologists nor pharmacists questioned here thought the drug was prescribed in an unusual manner.

Conclusion

Anaphylactoid reactions to tolmetin are manifested by clinical features varying from diffuse erythema and pruritus only to a generalized maculopapular eruption with combinations of urticaria, wheezing and syncope occurring shortly after ingesting a single capsule. They occurred in patients who had interrupted a previous course by at least three days. The patients did not have asthma or atopy. They were able to tolerate aspirin and other NSAIDs not closely related chemically. Neither an IgE-mediated nor anaphylotoxic pathogenesis could be established, but our studies were not exhaustive.

Physicians should be aware that at the start of a second course of tolmetin, severe immediate reactions may occur. There is no criterion to predict susceptible persons with the exception of a prior reaction to zomepirac. In those who have had an anaphylactoid reaction and who continue to require NSAIDs, an aspirin challenge study can be considered. Until the safety of related indole acetic acid analogues can be established, recourse to less related classes of NSAIDs (fenamates, pyrazolones, oxicoms and acetylsalicylates) appears to be preferable.

Addendum

An eighth case was encountered after this paper was submitted for publication. A 43-year-old woman had an acute episode of angioedema, erythroderma and pruritus, tachycardia, tremor and near syncope 30 minutes after ingesting a tolmetin capsule. One capsule three months earlier had produced transient urticaria, whereas no reactions occurred during her initial dosing for one week a month before that. There was no eosinophilia or history of atopy. No intolerance appeared to aspirin or ibuprofen before or to aspirin after the anaphylactic episode.

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Asbestos and Gastrointestinal Cancer

A Review of the Literature

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Exposure to asbestos is among several factors cited as possible causes of esophageal, gastric and colorectal cancer. More than 45 published studies have presented mortality data on asbestos-exposed workers. For each cohort, we listed the observed and expected rates of deaths from types of gastrointestinal cancer based on the latest published follow-up. Summary standardized mortality ratios (SMRs) were then derived. Finally, we calculated summary SMRs for total gastrointestinal tract cancer for three occupational groups: asbestos factory workers, insulators/shipyard workers and asbestos miners.

Statistically significant elevations in summary SMRs were found for esophageal, stomach and total gastrointestinal tract cancer in all asbestos-exposed workers. Esophageal cancer summary SMR remained significantly elevated when data were reanalyzed to include only those cohorts with death certificate diagnoses for cause of observed deaths. However, summary SMRs were not statistically significant for stomach and total gastrointestinal tract cancer after reanalysis. Summary SMRs by occupational group showed a significant elevation for total gastrointestinal cancer in insulators/shipyard workers. The elevation was not significant after reanalysis.

Based on the results after reanalysis, the elevations in summary SMRs for stomach and total gastrointestinal tract cancer are of a magnitude that could result from diagnostic and investigator error. We conclude that more studies are required before stomach and colorectal cancers are documented as asbestos-related diseases.

(Morgan RW, Foliart DE, Wong O: Asbestos and gastrointestinal cancer—A review of the literature. West J Med 1985 Jul; 143:60-65)

What causes gastrointestinal cancer is far from clear. Cited as possible causes are factors as diverse as diet, race, blood group, alcohol intake and exposure to asbestos. This review will examine the relationship of occupational asbestos exposure to the risk of developing carcinoma of that portion of the gastrointestinal tract including the esophagus, stomach and colon-rectum. The association of asbestos and peritoneal mesothelioma is well documented, does not involve the gastrointestinal tract and will not be reviewed here.

Esophageal cancer is a relatively uncommon cancer for which death rates have remained stable over time: 4.1/100,000 in 1955 and 4.3/100,000 in 1975, for US white men. Higher death rates have been reported in areas of Africa and Eastern Europe. In the United States, esophageal cancer is found predominantly in men and is associated with cigarette smoking and alcohol intake.

Gastric cancer is a slightly more common disease of considerable geographic variation, with some countries, notably Japan, having rates significantly higher than those of the United States. Dietary factors have been implicated in the pathogenesis of the disease. In the United States both mortality and incidence of stomach cancer in white men have fallen consistently and dramatically over a 20-year period. For example, the mortality rate dropped from 17.2/100,000 in 1955, to 8.2/100,000 in 1975.

Colorectal cancer presents an etiologic puzzle distinguished more by the number of hypotheses than by discovery of causative agents. In addition to asbestos, associations are postulated for intake of fiber, fat and specific foodstuffs. For US white men, death rates for colorectal cancer were 23.4/100,000 in 1955 and 24.4/100,000 in 1975.

Attempts to study the relationship of asbestos to gastroin-

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ABBREVIATIONS USED IN TEXT

AR = attributable risk
SMR = standardized mortality ratio

testinal cancer are frustrated by a number of factors. First, for any specific site (for example, stomach), the disease is sufficiently uncommon that few work forces can be expected to account for enough cases from which to draw conclusions. Perhaps more important, there is considerable opportunity for misdiagnosis or inaccurate certification of death, in that some gastrointestinal tract cancers will be certified as mesothelioma, and vice versa. This question has been addressed by both Newhouse [1] and Selikoff [2] in their examinations of death certificate accuracy in asbestos workers' deaths. In the Newhouse series, half of the deaths certified as gastrointestinal cancer were actually due to mesotheliomas. In Selikoff's series, only 24 deaths were originally certified as peritoneal mesotheliomas; after examining further clinical and pathologic evidence from other deaths in the cohort, investigators classified 112 deaths as due to that cause, with a pronounced reduction in number of deaths due to "all other cancer" and "all other causes."

Although diagnostic inaccuracy is troubling, it is not easily remedied. Selikoff has used "best evidence" from numerous sources, rather than the certified cause of death, to calculate standardized mortality ratios (SMRs). However, "best evidence" data cannot properly be compared with national mortality statistics, which are derived solely from death certificates. Unless one can also correct the statistics from the US reference population, comparisons are invalid because of the underlying principle that both study and reference populations should have similar ascertainment and classification of death. Another statistically questionable practice is attributing to cancer those deaths previously certified as due to a cause other than cancer, but where cancer was present (Selikoff communication quoted by Miller[3]). Again, without a similar mechanism for including cancer as a contributing cause of death in the national mortality statistics, such comparisons will either create an apparent excess of cancer in the study population or will exaggerate any excess already there.

Most of the evidence concerning asbestos and disease comes from the retrospective cohort mortality studies of asbestos-exposed workers. In all of these studies, a cohort exposed to asbestos has been identified from employment, union or other existing records and then followed prospectively over time to compare their rate and pattern of mortality with a reference population with presumably no exposure or less exposure. The reference population is frequently that of county, state or country. In general, national statistics are used because of availability and the stability imparted by large numbers. Smaller jurisdictions tend to produce statistics that can be heavily influenced by relatively few deaths, including those occurring in the work force under study.

Methods

To determine the role of occupational asbestos exposure in the risk of gastrointestinal cancer, we attempted to identify all relevant publications from the indexed literature. From each report, we extracted the details concerning cohort definition, exposure of concern and gastrointestinal cancer deaths (both observed and expected). We did not include any judgment concerning scientific merit in selecting papers to be included.

A summary of published studies of asbestos-exposed workers is presented in Table 1. Some 45 publications have described about 22 different cohorts, although within them there is some overlap. Deciphering the interwoven cohorts is complicated because in many cases a single data set has been repeatedly published, sometimes for an alternative analysis. In other cases, there appears to be no clear reason for the republication. Further confusion is introduced when papers do not specify that the data, or portions thereof, were previously reported. Some of the cohort studies reported do not mention gastrointestinal cancer, let alone specific sites, so contribute little to a quantitative analysis.

Table 2 summarizes the results of those studies which are informative as to the possible relationship of asbestos to gastrointestinal cancer. Studies were included in Table 2 when the number of gastrointestinal tract cancer deaths was available and the cohort discrete. Because of the problem of data overlap, we have used the latest published follow-up of each cohort rather than numbers from earlier papers. When available, observed deaths based on death certificates, rather than "best evidence," are presented in Table 2. Several of the studies[24,28,38] in Table 2 grouped deaths from peritoneal mesotheliomas with gastrointestinal cancers. When the actual numbers of mesotheliomas were given in the text, we deleted these from "observed" deaths. One report[33] grouped esophageal and stomach cancer deaths together for analysis. This report was not included in the calculations for those sites.

In order to provide a quantitative summary risk index for gastrointestinal cancers based on the studies reviewed, we have examined a number of statistical procedures. One procedure is the combination of relative risks based on the variance-weighted logarithms of the relative risk.[56-58] In this procedure, we can treat each cohort as a 2×2 table and the SMR as a special type of relative risk.[59] The unexposed group in the 2×2 table would be a sample of the standard population, whose sample size is the same as that of the exposed study group. This procedure, however, presents some difficulties because the number of person-years is not always presented in every study reviewed.

Another procedure of combining the risk estimates from these studies is the indirect standardization. We can view each cohort as a separate stratum; within each, certain characteristics are homogeneous (for example, study design, length of follow-up and exposure). This view is similar to that in calculating SMR within a cohort, where the strata are homogeneous with respect to age, race, sex and so forth. In the direct standardization only the observed and expected deaths are needed for the calculation. The summary SMR can be calculated as follows:

$$\text{Summary SMR} = \frac{\text{Sum of Observed Deaths}}{\text{Sum of Expected Deaths}} \times 100.$$

In essence, the summary SMR is weighted by the number of expected deaths, which is the reciprocal of the variance of the individual SMR.[58] Thus, this method is, to some extent, similar to the one based on the logarithm of the relative risks.

Needless to say, this application of the indirect standardization in summarizing SMRs from different studies is subject to the same criticisms that are often raised in summarizing

age-sex-race-specific rates in a single study. On the other hand, we know of no way to overcome the bias due to the fact that negative studies were less likely to result in published SMRs or observed and expected values, although even studies with negative findings in gastrointestinal cancer but with positive findings in respiratory tract cancer would still have a high likelihood of being published.

We have also derived summary SMRs for three major occupations: asbestos factory workers, insulators/shipyard workers and miners. In the follow-up of the New York-New Jersey cohort of insulation workers to 1976,[2] only "best evidence" calculations of observed deaths are presented (Table 3). Due to the limitations of "best evidence" data, summary SMRs were also calculated after deleting observed deaths in this cohort.

Results

Summary SMRs and confidence intervals for esophageal, stomach, colorectal and total gastrointestinal tract cancer appear in Table 3. Significant elevations in summary SMRs

TABLE 1.—*Summary of Studies of Asbestos-Exposed Workers*

Authors	Published: First	Published: Follow-up	Date Re-published	Cohort Description and Comments
Doll	1955 (9)*	...	...	Asbestos textile factory workers
Knox et al	...	1965 (10)	...	Followed through 1961
		1968 (11)	...	Followed through 1966
Peto et al	...	1977 (12)	...	Followed through 1974
Braun and Truan	1958 (14)	...	...	Canadian asbestos miners followed 1950-55
Dunn et al	1960 (15)	...	...	Multiple occupational groups studied 1954-62
		1965 (16)	...	Follow-up through 1962
Mancuso et al	1963 (17)	...	...	Factory workers followed 1938-60
	1967 (18)	...	...	Same cohort?
Elwood et al	1964 (19)	...	...	Asbestos sheeting factory workers followed 1936-62
Selikoff et al	1964 (5)	...	1979 (2)	New York-New Jersey insulators followed through 1962
		1968 (6)	...	Followed through 1964
		1974 (4)	...	Followed through 1971
		1979 (2)	1981 (52)	Followed through 1976
Selikoff et al	1972 (20)	...	...	Asbestos insulation workers, including NY-NJ cohort survivors, followed through 1971
		1979 (2)	1979 (50)	Followed to 1976
			1981 (52)	...
Selikoff et al	1972 (21)	...	...	Amosite factory workers through 1971
		1979 (49)	1980 (22)	Followed through 1977
			1981 (51)	...
Selikoff et al	1979 (7)	...	...	Shipyard workers from 1967-76, a subcohort of 1972a study
Selikoff et al	1979 (8)	...	...	Chrysotile miners from Quebec
Enterline	1965 (23)	...	...	Asbestos products workers 1948-51, followed through June 1963
	1967 (24)	...	...	Asbestos products workers to 6/30/63, some from previous cohort
Kleinfeld et al	1967 (25)	...	...	PMR study of asbestos workers
Newhouse et al	1969 (1)	...	...	Asbestos factory men
	1972 (26)	...	...	Asbestos factory women employed 1936-1942, followed through 1968
	1973 (27)	...	...	Follow-up of above 2 cohorts to 1970
	1979 (28)	...	...	Follow-up to 1975
Elmes and Simpson	1971 (29)	...	...	170 Shipyard workers through 1966
		1977 (30)	...	Followed through 1975
McDonald et al	1971 (31)	...	...	Quebec miners followed to 11/1/66
		1974 (32)	...	Followed through 1969 with different analysis
		1980 (33)	...	Followed through 1975
	1978 (34)	...	...	199 Exposed to crocidolite traced through 1975
Enterline	1972 (35)	...	...	Retirees from asbestos mfg followed through 1969
			1973 (36)	Retirees presumed identical to the above
			1973 (37)	Reanalysis of previous two papers
		1979 (38)	...	Retirees followed through 1973
Meurman et al	1974 (39)	...	...	Case-control study of anthophyllite miners
Weiss	1977 (40)	...	...	Chrysotile factory workers 1935-54 followed through 1974
Rubino et al	1979 (41)	...	...	Miners followed through 1974
Gillam et al	1979 (42)	...	...	Gold miners exposed to asbestiform rock followed through 1973
Kolonel et al	1980 (43)	...	...	Shipyard workers followed through 1969
Jones et al	1980 (44)	...	...	Gas mask workers followed through 1978
Hobbs et al	1980 (45)	...	...	Crocidolite miners followed through 1978
Rossiter and Coles	1980 (46)	...	...	Dockyard workers 1947-78
Hughes and Weill	1980 (13)	...	...	Factory workers followed through 1974
Newhouse and Berry	1982 (47)	...	...	Asbestos (mainly chrysotile) friction material workers, 1942-79
		1983 (48)	...	Followed through 1980
Acheson et al	1982 (53)	...	...	Female gas mask workers, 40-year follow-up

PMR=proportionate mortality ratio

*Numbers in parentheses ( ) = reference numbers.

were found for esophageal (SMR = 214) and gastric (SMR = 183) cancer. Although summary SMRs for these sites were based on data from four studies, numbers were small and the 95% confidence intervals were wide. The slight excess in SMR for colorectal cancer (SMR = 113) was not statistically significant. The SMR for total gastrointestinal tract cancer (SMR = 108) was minimally but significantly elevated.

Table 4 presents site-specific summary SMRs after "best evidence" data are deleted. Esophageal cancer remains elevated (SMR = 238, $P < .05$).

Total gastrointestinal tract cancer deaths and summary SMRs for three exposure categories are presented in Table 5. Of the three occupational groups, only insulators/shipyard workers had a significant elevation in total gastrointestinal tract cancer (SMR = 132). Total gastrointestinal tract cancer was not significantly elevated in insulators when "best evidence" data were removed.

Discussion

The strongest evidence linking asbestos to esophageal and gastric cancer is a series of studies of the New York-New Jersey (NY-NJ) and US-Canadian insulation workers.[2,4-6] The summary SMR for esophageal cancer was significantly

TABLE 2.—*Summary of SMRs from Various Cohort Studies*

Author (Date)/Comments	(Ref. No.)	Cohort Size	Person-Years	Standard Population	Esophageal Cancer			Stomach Cancer			Colorectal Cancer			Total GI Cancer		
					SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp
Peto et al (1977) Asbestos factory workers	(12)	1,106	16,072	Brit Natl	...	...	...	...	...	...	...	...	...	102	16	15.7
Selikoff et al (1979) NY-NJ insulators to 1976 ("best evidence" used)	(2)	632	13,925	US	71	1*	1.4	352	19*	5.4	277	23*	8.3	285	43*	15.1
Selikoff et al (1979) US-Canada insulators	(2)	17,800	166,853	US	253	18	7.1	127	18	14.2	152	58	38.1	158	94	59.4
Selikoff et al (1980) Amosite factory workers	(22)	582	6,311	New Jersey	125	1	0.8	200	4	2.0	212	11	5.2	200	16	8.0
Selikoff et al (1979) Shipyard workers	(7)	389	...	US	...	...	...	...	...	...	...	...	...	97	3	3.1
Nicholson et al (1979) Chrysotile mining and milling	(8)	544	7,408	Canada Natl	...	...	...	...	...	...	...	...	...	105	10	9.5
McDonald et al (1980) Chrysotile miners, 20 or more years after 1st employment; stomach/esophageal deaths analyzed together	(33)	11,379	...	Quebec	127	130*	102.0	127	130*	102.0	78	79	101.0	103	209	202.9
Newhouse and Berry (1979) Rates exclude mesotheliomas	(28)	5,522	...	Brit	...	...	...	...	...	...	...	...	...	136	60*	44.2
Enterline and Kendrick (1967) Various exposures (bldg, friction/textile products), rate includes malignant mesotheliomas	(24)	21,755	...	US	...	...	...	...	...	...	...	...	...	106	83	78.2
Henderson and Enterline (1979) Rates include mesotheliomas	(38)	1,348	...	US	...	...	...	...	...	...	...	...	...	138	110	79.7
Meurman et al (1974) Anthophyllite miners	(39)	1,092	...	Finland	...	...	...	...	...	...	...	...	...	47	7	14.9
Weiss (1979) Chrysotile miners; stomach & colorectal cancers combined to calculate GI cancer SMR	(40)	264	...	US	...	...	...	...	...	...	...	...	...	105	4	3.8
Rubino et al (1979) Chrysotile miners	(41)	952	21,459	Italy	...	...	...	...	...	...	...	...	...	98	19	19.4
Jones et al (1980) Gas mask workers	(44)	951	...	Brit	...	...	...	...	...	...	...	...	...	49	10	20.4
Rossiter and Coles (1980) Shipyard workers	(46)	6,292	...	Engl/Wales	...	...	...	...	...	...	...	...	...	83	63	75.9
Hughes and Weill (1980) Factory workers	(13)	5,645	...	US	...	...	...	...	...	...	...	...	...	50	25	50.0
Mancuso and Coulter (1963) Factory workers	(17)	1,495	23,257	US	200	1	0.5	107	2	1.9	145	5	3.5	135	8	5.9
Berry and Newhouse (1983) Asbestos friction materials (mainly chrysotile) workers	(48)	11,182	163,009	Engl/Wales	...	...	...	...	...	...	...	...	...	98	132	134.6

GI = gastrointestinal, SMR = standardized mortality ratio

*See comment in Author (Date)/Comments column

elevated even after "best evidence" data on observed deaths in the New York-New Jersey cohort were removed. Gastric cancer in the NY-NJ cohort contributed 19 observed deaths of 43 deaths in the calculation of the summary SMR. For the NY-NJ cohort, unfortunately, causes of death used in analysis were obtained not only from death certificates but from "best evidence." The authors did not present the number of observed deaths derived solely from death certificate information. The gastric cancer summary SMR was not significantly elevated when "best evidence" data were deleted. The same researchers found no excess of gastrointestinal cancer in either shipyard workers[7] or chrysotile miners.[8] One of the best-performed and longest-term cohort studies[9-12] has found no increase of gastrointestinal cancers of any type after more than 50 years of meticulous follow-up from first exposure.

Most of the evidence favoring an association between asbestos and gastrointestinal cancer comes from a series of studies by one group of investigators; these results must withstand critical review if a causal relationship is to be accepted. The fallacy of using "best evidence" for the cause of death has been discussed above, as a bias that inflates SMRs. In addition, repeated publishing of the same results may have created the illusion of more positive evidence than actually exists. Four cohorts have resulted in at least 14 publications (see Table 1). The original table describing the original New York-New Jersey cohort, first published in 1964, was republished in 1979 without incorporating the follow-up that had been accomplished and published in the interim. The 1976 follow-up was published in both 1979 and 1981. The 1976 follow-up of the US-Canadian cohort was published twice in 1979 and the amosite cohort follow-up of 1977 was published in 1979, 1980 and 1981. The negative studies[7,8] have not been republished.

In an earlier review, Miller[3] came to the conclusion that asbestos and gastrointestinal malignant conditions were causally related, although he did not attempt to calculate a summary risk estimate. Most of his conclusions were based upon the work of Selikoff and the review did not have the later negative studies coming from Peto,[12] Hughes[13] and Selikoff's associates.[7,8] Miller also failed to appreciate the error involved in the practice of using "best evidence" rather than the certificated cause of death for comparison with national statistics. Finally, although the review paper acknowledges the work by Newhouse in showing the extent of cause-of-death

TABLE 3.—*Summary SMRs*

Site of Cancer	*Observed*	*Expected*	*SMR*	*95% Confidence Interval**	*References*
Esophagus	21	9.8	214†	132.6-327.6	2‡,17,22
Stomach	43	23.5	183†	132.4-246.5	2‡,17,22
Colorectal	176	156.4	113	96.5-130.4	2‡,17,22,33
Total gastrointestinal tract	912	840.9	108†	101.5-115.7	2‡,7,8,12,13,17,22,24,28,33,38,41,44,46,48

SMR=standarized mortality ratio

*Reference 54.
†$P < .05$.
‡NY-NJ cohort and US-Canadian cohort.

TABLE 4.—*Summary SMRs Deleting 'Best Evidence' Data*

Site of Cancer	*Observed*	*Expected*	*SMR*	*95% Confidence Interval**	*References*
Esophagus	20	8.4	238†	145-368	2‡,17,22
Stomach	24	18.1	133	85-197	2‡,17,22
Colorectal	153	148.1	103	88-121	2‡,17,22,33
Total gastrointestinal tract	869	825.8	105†	98-113	2‡,7,8,12,13,17,22,24,28,33,38-41,44,46,48

SMR=standardized mortality ratio

*Reference 54.
†$P < .05$.
‡US-Canadian cohort; NY-NJ cohort excluded.

TABLE 5.—*Summary SMRs By Occupation for Total Gastrointestinal Tract Cancer*

Occupation	*Observed*	*Expected*	*SMR*	*95% Confidence Interval**	*References*
Asbestos factory workers	460	436.9	105	95.9-115.4	12,13,17,22,24,28,38,44,48
Insulators/shipyard workers	203	153.5	132†	114.7-151.7	2‡,7,46
Insulators/shipyard workers deleting "best evidence" data	160	138.4	116	98.0-135.0	2§,7,46
Asbestos miners	249	250.5	99	87.4-112.5	8,33,39,40,41

SMR=standardized mortality ratio

*Reference 54.
†$P < .05$.
‡NY-NJ cohort and US-Canadian cohort.
§US-Canadian cohort;NY-NJ cohort excluded

misclassification, there was little attention paid to its potential impact on study results.

Conclusion

Malignant lesions of the lung, pleura and peritoneum have been clearly linked with exposure to asbestos. Some studies of cohorts occupationally exposed to asbestos have also found elevations in incidence of gastrointestinal cancer, while other reports have not found excesses after years of follow-up.

In an effort to summarize the available studies of gastrointestinal cancers in asbestos-exposed workers, we have calculated summary SMRs for esophageal, gastric, colorectal and total gastrointestinal tract cancer. In addition, we have derived total gastrointestinal tract cancer summary SMRs for workers exposed to asbestos in three specific capacities: factory work, shipyard/insulation work and mining.

Although there are statistically significant elevations of SMR for esophageal and gastric cancer for all groups and for total gastrointestinal tract cancer for insulators and shipyard workers, we are not convinced of the relationship to asbestos exposure, especially for stomach cancer, where the finding is inconsistent and possibly erroneous in the largest positive study. For colorectal cancer, at this time there is no discernible relationship to asbestos exposure. We hope that the occupationally exposed cohorts now under study will provide more conclusive evidence soon—refuting or supporting such an association.

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Squamous Carcinoma of the Nasopharynx

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Nasopharyngeal carcinoma is an unusual neoplasm among squamous cell carcinomas of the head and neck. The tumor is rare in most parts of the world but is strikingly common in several Asian subpopulations, notably Chinese in Hong Kong and Guangdong Province. The Epstein-Barr virus is intimately related to the disease and elicits the formation of antibodies that are useful for diagnosis and follow-up study. The virus has not been conclusively shown to cause nasopharyngeal cancer, however.

Histologically, nasopharyngeal carcinoma is anaplastic in 75% of cases and better differentiated in 25% of patients. All tumors are treated by high-dose irradiation to the primary site and both sides of the neck. Surgical treatment, in the neck only, is reserved for irradiation failures. The prognosis is better in patients younger than 40 years, in patients without clinical cervical nodal involvement and, unexpectedly, in patients with anaplastic tumors.

(Moloy PJ, Chung YT, Krivitsky PB, et al: Squamous carcinoma of the nasopharynx [Medical Progress]. West J Med 1985 Jul; 143:66-69)

Nasopharyngeal carcinoma is an unusual neoplasm among squamous cell carcinomas of the head and neck. The tumor has a distinctive geographic and ethnic incidence and an intriguing but ambiguous relationship with the Epstein-Barr virus (EBV). Histologically the tumor is usually anaplastic or poorly differentiated, often with an intense infiltration of benign lymphocytes (lymphoepithelioma). Treatment of the primary lesion in the nasopharynx is by irradiation alone and treatment of the neck node metastasis is by irradiation and surgical removal. We review these factors and present an interesting case.

Incidence

Nasopharyngeal carcinoma is a rare neoplasm in most parts of the world, constituting less than 0.3% of all malignant tumors and only 2% of all head and neck cancer.[1] It is, however, one of the most frequently occurring cancers among certain people of South Chinese origin, specifically those from Hong Kong and Guangdong Province (formerly, Kwangtung Province and Kwangsi Province). The disease is responsible for 57% of all cancers in men and 17% of all cancers in women in these areas according to biopsy data.[2] The highest incidence is reported in boat people living along the South China coast.[3]

Nasopharyngeal carcinoma occurs frequently in Alaskan native peoples (Eskimo, Aleut, Indian)[4] and among people of southern Chinese origin living in several other Southeast Asian countries, in California, in Honolulu and in British Columbia.[5] The risk of nasopharyngeal carcinoma developing in these populations remains high for several generations despite emigration from endemic areas. Analyzing mortality data for nasopharyngeal carcinoma in the San Francisco-Oakland area from 1958 to 1972, Buell[6] found the incidence in third-generation Chinese to be less than that in southern China, but ten times greater than that in whites.

Nasopharyngeal carcinoma is rare in whites. The disease is similarly rare in Japanese, Koreans and most blacks except for certain areas in Africa (Uganda, Tunisia) where an intermediate frequency exists.[7] It is infrequent in Indians in Singapore and Malaysia. In all population studies and whether there is a high or a low overall incidence, nasopharyngeal carcinoma is three times more common in men than in women. The significance of this sex difference is unknown. The age distribution of nasopharyngeal carcinoma is younger than for other squamous carcinomas of the head and neck and 15% to 20% of cases are younger than 30 years at onset.

Epidemiologic data are summarized in Table 1.

Etiology

Despite the high incidence of nasopharyngeal carcinoma in certain southern Chinese, the disease is not linked to the Mongoloid race per se as it occurs in non-Mongoloids and is

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
EBV = Epstein-Barr virus

notably rare in several large groups of Mongols such as the Japanese. The high incidence of this cancer in southern Chinese and, particularly, in the South China coast boat people, has been attributed to the consumption of large amounts of salted fish and a vitamin C-deficient diet early in life.[3,4,8,9] An association with diet is interesting because it has been shown that carcinoma of the nasal and paranasal regions can be experimentally induced in animals fed large quantities of salted fish.[3]

The Epstein-Barr virus may play a role in the pathogenesis of nasopharyngeal carcinoma, although a causal relationship has not been conclusively shown despite intensive investigation. Data concerning antibody titers to various fractions of EBV are interesting and may provide a means of following selected patients who have nasopharyngeal carcinoma once the condition is diagnosed (see below).

Pathologic Features

According to the most recent World Health Organization system of classification,[10] nasopharyngeal carcinoma is divided into three types: keratinizing squamous cell carcinoma, nonkeratinizing carcinoma and undifferentiated carcinoma. All three types are derived from squamous cells, although epithelial cellular differentiation by light microscopy is evident only in keratinizing squamous cell carcinoma. Electron microscopy has shown a squamous cell derivation for nonkeratinizing and undifferentiated carcinomas by consistently showing desmosomes, or intercellular bridges, and tonofilaments[11]—hallmarks of squamous cells. Tumors from individual patients are classified according to the dominant and histologic type, although features of more than one type may be present. Infiltration by mature lymphocytes is common in all three types of nasopharyngeal carcinoma, particularly in the nonkeratinizing and undifferentiated forms, and led to the earlier designation of lymphoepithelioma for these tumors. The presence of a large number of lymphocytes may represent a host immune response to the carcinoma.[11] The presence or absence of lymphocytes, however, does not influence five-year survival figures, although at three years tumors with lymphocytic infiltration seem to respond to treatment better than tumors without lymphocytic infiltration.[11]

The more anaplastic tumors (the nonkeratinizing and undifferentiated varieties) are more common than better differentiated tumors (keratinizing squamous cell variety) and together account for 75% of cases. This is true for all populations surveyed. That is, the relative proportions among cases of keratinizing squamous cell carcinoma (15% to 20%), nonkeratinizing carcinoma (40%) and undifferentiated carcinoma (40%) are similar among south Chinese, who are at high risk, and among whites and Japanese, who are at low risk for nasopharyngeal carcinoma.[11]

The histologic classification of nasopharyngeal carcinoma may be an important prognosticator of patient survival. Patients with undifferentiated tumors have been reported by some authors to have a greater likelihood of surviving five years than do patients with better differentiated tumors.[5] Other studies, however, indicate that nasopharyngeal carcinoma is a fairly uniform disease despite histologic variation and that the dominant cell type does not influence prognosis.[12,13]

TABLE 1.—*Incidence of Nasopharyngeal Squamous Cell Carcinoma per 100,000 Population per Year*

Location (No. of Patients)	*Men*	*Women*	*Combined*
Vancouver, white population (5)	...	...	0.23
San Francisco-Oakland, white population (7)	...	...	0.9
North American white, Connecticut (7)	0.17	0.05	0.22
European white, Norway (7)	0.16	0.09	0.35
Japanese, Korean	1 to 2	0.4	...
California, Filipino (6)	1.8	...	...
Los Angeles, Filipino (9)	3.6	...	...
San Francisco-Oakland, Chinese (6)	17.8	...	...
Singapore, Chinese (7)	20.2	9.0	...
Hong Kong, Chinese (3)	35.5	15.1	...
Hong Kong, Chinese boat people (3)	54.7	18.78	...
Vancouver, Chinese (5)	...	...	27.12
Tunisia, blacks (7)	7.5	3.3	...
Alaskan native population (4)	13.5	3.7	...

TABLE 2.—*Presenting Symptoms and Signs Among 99 Patients With Nasopharyngeal Carcinoma**

Symptom	*Percent*
Hearing loss	48
Cervical mass	57
Nasal obstruction	29
Otitis media	36
Epistaxis	22
Pain	15
Headache	12

*Modified from Baker and Wolfe.[13]

Symptoms

Patients present with the symptoms to be expected from a rapidly enlarging lesion in the nasopharynx (Table 2). Local symptoms include conductive hearing loss due to serous otitis media caused by tumor obstructing the eustachian tube, epistaxis and nasal obstruction. These symptoms in an adult, especially unilateral serous otitis media, should be assumed to be due to nasopharyngeal carcinoma until proved otherwise.

About 60% of patients present with metastasis to cervical lymph nodes, particularly upper jugular nodes and posterior triangle nodes. Metastatic lesions in cervical nodes are usually large, often much larger in fact than the primary lesion in the nasopharynx.

Nasopharyngeal carcinoma grows readily along the base of the skull and can involve several cranial nerves early in the course of illness (most commonly, nerves V, VI, IX, X, XI and XII). Direct intracranial extension via these cranial nerves and the foramina through which they pass is a particularly common growth pattern (see Report of a Case below). Patients occasionally present with evidence of distant metastasis, usually to lung or bones, along with local symptoms in the nasopharynx.

Diagnosis and Staging

Diagnosis requires histologic documentation by biopsy and staging relies importantly on radiographic studies to de-

fine the extent of disease. Multiple plain radiographs (including axial views) permit the diagnosis in most instances, but in all cases the computed tomographic (CT) scan will yield valuable information.[14] The CT scan can show the extent of soft tissue involvement in the neck and unsuspected central nervous system extension from the nasopharynx. In addition, the CT scan is more sensitive for detecting small primary lesions in the nasopharynx than physical examination or plain radiographs. Complete radiographic studies including CT scan should be done before a biopsy because the biopsy procedure itself leads to edema and inflammation that will distort radiographic findings for several weeks.

Relationship of Epstein-Barr Virus to Nasopharyngeal Carcinoma and Serologic Tests

The EBV is a small DNA virus resembling the herpes simplex virus. It has been proved to be the causative agent of infectious mononucleosis and African Burkitt's lymphoma. The EBV may play an important role in the pathogenesis of the undifferentiated varieties of nasopharyngeal carcinoma. This possibility is supported by the finding that serum specimens from most patients with nasopharyngeal carcinoma contain antibodies to EBV antigens.[14] These antibodies are found in all populations, not just southern Chinese. The incidence of "false-positive" anti-EBV antibody titer elevation is 5% or less among healthy volunteers and patients with other head and neck squamous cancers.[15]

Anti-EBV antibody profiles correlate well with undifferentiated and nonkeratinizing tumors but not with keratinizing tumors. This is not surprising because the EBV itself has not been found in association with keratinized, well-differentiated nasopharyngeal carcinoma with any regularity, but is almost always found in patients with the undifferentiated types of nasopharyngeal carcinoma.

Henle and Henle[16] have shown that rising anti-EBV antibody levels may signal recurrence of tumor before it is clinically evident. The same investigators have also shown that, in untreated patients, antibody titers increase as the stage of the disease advances. Titers rise especially as the tumor burden increases in the form of distant metastasis.

These data are of clinical importance. Early identification of residual or recurrent tumor is difficult to detect clinically and serologic testing may aid in the diagnosis before the disease is clinically apparent and while the tumor burden is small. Serologic testing may also be helpful in identifying nasopharyngeal carcinoma as the source in patients who present with a lump in the neck of occult origin.[16]

Treatment and Prognosis

Treatment of a primary lesion in the nasopharynx and of all direct extensions from the primary is by radiotherapy. From 6,500 to 7,000 rads are delivered by external beam through portals that include all of the nasopharynx, adjacent skull base to the level of the sella turcica and cervical lymph nodes (both sides).[18] Patients with cervical nodes clinically showing metastasis also receive 6,000 rads to lower cervical and upper mediastinal nodes.

Unlike other squamous carcinomas of the head and neck, cervical node metastasis in cases of nasopharyngeal carcinoma usually responds favorably to radiotherapy.[15] Surgical treatment in the form of radical neck dissection is used only in relatively uncommon cases in which patients are not cured by radiotherapy and in patients in whom regional nodal disease develops following a course of irradiation.

The overall five-year cure rate is about 50%.[18] Survival is distinctly better in younger adults (age, 20 to 49) than in persons older than 50 years.[5] Cure rates do not correlate closely with the presence or absence of clinically positive lymph nodes unless the nodal disease is advanced.[13] Survival does correlate with the extent of local tumor invasion,[17] and small lesions (stages T_1 and T_2) have an overall five-year cure rate of 60% versus 44% for larger (stages T_3 and T_4) lesions.[13] Most important, cure rates for anaplastic carcinomas (nonkeratinizing and undifferentiated) are consistently reported to be better than for well-differentiated (keratinizing squamous cell) carcinoma. Dickson[5] reports five-year cure rates of 42% to 52% for nonkeratinizing and undifferentiated carcinomas versus 22% for keratinizing squamous cell carcinoma.

Report of a Case

The patient, a 39-year-old Filipino man, presented in 1969 with a two-week history of right-sided hearing loss and occasional mild epistaxis. A small T_1 lesion was found in the right lateral nasopharynx on indirect mirror examination. No adenopathy was felt in the neck. Biopsy specimens from the nasopharynx showed undifferentiated squamous carcinoma with moderate lymphocytic infiltration. Treatment consisted of the administration of 5,500 rads to the nasopharynx and both sides of the neck.

He was asymptomatic until 1977 when diplopia on right lateral gaze was noted. Paresis of the right true vocal cord developed the following year along with absent gag reflex. In 1979-1980 paralysis of the right side of the tongue was noted. On examination of the nasopharynx, neck and lungs, no abnormalities were found and CT scans done in 1979 and 1980 were negative. The patient was initially thought to be suffering from a radiation-induced cranial neuropathy. In 1981, however, a repeat CT scan showed multiple intracranial masses involving all three cranial fossae, especially in the cavernous sinus area (Figure 1). A biopsy of the nasopharynx was done on several occasions with negative results. A transsphenoidal biopsy specimen was then obtained that showed poorly differentiated squamous carcinoma, which was identical to the original tumor found in 1969.

The patient was given 5,040 rads via lateral brain ports. He died five months later of aspiration pneumonia. An autopsy showed good response of tumor in the central nervous system, but malignant cells were identified in the right sigmoid sinus, the right trigeminal nerve root and in the ventral right cerebellum. There was no evidence of distant metastasis.

Comment

The tumor in this man was slow growing despite anaplastic morphology and remained radiosensitive for many years. It was locally invasive for 13 years without regional or distant metastasis. Eventually, however, tumor spread into all three cranial fossae by direct extension through foramina in the base of the skull (Figure 2). In retrospect, we think that serial antibody titers to EBV might have led to an earlier diagnosis of local recurrence. It is impossible to know if the

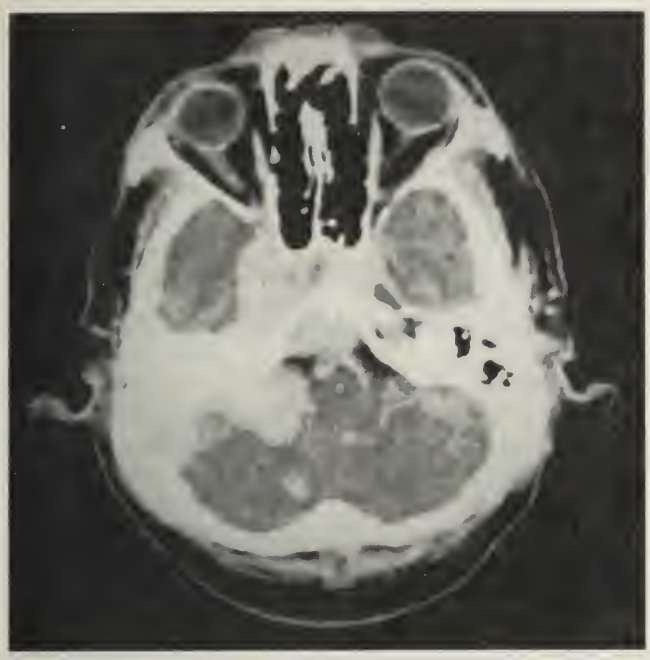

Figure 1.—Computed tomographic scan of the head showing multiple intracranial implants.

Figure 2.—Large anatomic cleft at the base of the skull (arrow). This cleft extends from the jugular foramen to the foramen lacerum and includes the petrosquamous suture. Nasopharyngeal carcinoma can invade through this area easily without producing radiographically detectable bony erosion.

tumor cells can persist for as long as one year following radiotherapy, especially in as slow growing a tumor as was present in this patient.

Summary

Nasopharyngeal carcinoma is common in people of southern Chinese origin and rare in most other racial groups. Although the cause is unknown at this time, the disease has been linked etiologically with the Epstein-Barr virus, with a diet high in salted fish and with vitamin C deficiency. Although the EBV has not been definitively shown to be a cause of nasopharyngeal carcinoma, antibodies develop to various fractions of the virus that fluctuate with interesting relationships to the course of illness in many patients.

The tumor may be histologically moderately well differentiated or well differentiated and show keratin pearl formation but more commonly is anaplastic. The histologic type bears on the prognosis because the five-year survival of patients with anaplastic tumors is better than that of better differentiated tumors, probably because of the greater radiosensitivity of anaplastic tumors to radiotherapy.

Diagnosis is based on tissue biopsy and staging on radiologic determination of the extent of tumor involvement (CT scan). Treatment of the primary neoplasm in the nasopharynx is with radiotherapy (6,500 to 7,000 rads by external beam). The neck is also treated with radiotherapy, with surgical intervention reserved for patients who have recurrence in the neck following radiotherapy.

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Nasopharyngeal Carcinoma

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Substantial advance has been achieved in our knowledge of nasopharyngeal carcinoma within the past two decades. Elsewhere in this issue Moloy and co-workers have presented a paper on the subject. I will present a review of the recent achievements and suggest goals for future research.

Pathology

There is no longer any disagreement that the predominant malignant tumor arising in the nasopharynx of people of all races is a carcinoma of the squamous cell type, although squamous differentiation may not be evident under light microscopy in a proportion of cases if only small biopsy specimens are available for examination. Under electron microscopy, however, features of squamous differentiation can be regularly detected even in such specimens. The nasopharynx is a part of the Waldeyer's lymphoid ring. Consequently, the presence of lymphocytes in the stroma of the primary tumor or its metastasis in lymph nodes is to be expected. In its metastasis in nonlymphoid tissue such as the liver, however, lymphocytes are either absent or scanty although features of the so-called lymphoepithelioma are present in the primary tumor and metastatic lesions of cervical lymph nodes.[1,2] Therefore, the degree of lymphocytic infiltration in biopsy specimens taken from the primary tumor or metastatic nodes cannot be taken to be a guide to prognosis. A nasopharyngeal or even a nodal biopsy specimen is only a tiny fraction of the whole disease, in which islands of keratinization may be found among sheets of anaplastic undifferentiated carcinoma cells, and approximately one quarter of classical squamous cell carcinomas show areas of undifferentiated structure.[3] It is, therefore, not unexpected that in careful studies of large series of cases neither the degree of lymphocytic infiltration nor the dominant histologic pattern has been found to be useful in indicating prognosis or in planning treatment.

Etiology

From current epidemiologic and experimental data the most tenable etiologic hypothesis is one that postulates the involvement of three major risk factors: (1) a genetically determined susceptibility that allows an Epstein-Barr virus (EBV) infection in early life of the type that permits (2) the integration of the genomes of the virus into the chromosomes of some nasopharyngeal epithelial cells, priming them for (3) neoplastic transformation by some environmental nasopharyngotropic carcinogen or carcinogens that have gained entry into the infected cells. Alternatively, the environmental agents may trigger the viral genome in the cells to oncogenic activity.[4] It must be said, however, that the only evidence suggesting that EBV may be a cofactor in the genesis of nasopharyngeal carcinoma is the regular finding of the DNA of the virus in undifferentiated and poorly differentiated nasopharyngeal cancer cells. Whether it plays a causal role or exists in the cells as a passenger is not known. The virus is ubiquitous, yet a high frequency of nasopharyngeal carcinoma is found only in certain ethnic groups. This suggests that whatever its role in the cause, it can only be a cofactor.

The etiology of nasopharyngeal carcinoma is very likely multifactorial; hence, as long as an environmental factor is an essential cofactor, prevention is possible. Epidemiologic data have favored ingestants rather than inhalants as likely risk factors in southern Chinese. Among ingestants salted fish (prepared by salting and drying) is most suspected to be a major risk factor.[5] It was until two to three decades ago traditionally fed to southern Chinese in Hong Kong from early childhood for economic reasons and taste. The suspicion of its causal role was first raised in 1971[6] and has received strong support from the findings of two recent case-control epidemiologic studies. In one study, 100 Chinese patients with nasopharyngeal carcinoma and 100 neighborhood controls in Malaysia were studied.[7] Analysis of the data showed that daily consumption of salted fish in childhood carried a relative risk of 17.4 (95% confidence interval = 2.7, 111.1) compared with nonconsumption. The other study involved 250 incident cases of patients younger than 35 years and an equal number of friend controls in Hong Kong. The data showed that the relative risk for consuming the food at least once a week compared with less than once a month at age 10 years was 37.7 (95% confidence interval = 14.1, 100.4) (M. C. Yu, J. H. C. Ho, S.H. Lai, et al, unpublished data*). Because the subjects were young, many had mothers who could be

*The survey itself was completed in November 1983. A preliminary report will appear in a National Cancer Institute monograph on the proceedings of the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16-20, 1984 (in press). The title of the paper is "The Epidemiology of Nasopharyngeal Carcinoma in Malaysia and Hong Kong" and the authors are M. C. Yu, J. H. C. Ho, B. E. Henderson and R. W. Armstrong.

(Ho JHC: Nasopharyngeal carcinoma [Editorial Comment]. West J Med 1985 Jul; 143:70-73)

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ABBREVIATIONS USED IN TEXT

AJC = American Joint Committee for Cancer Staging and End-Results Reporting
CT = computed tomography/ic
EBNA = nuclear antigen of the Epstein-Barr virus
EBV = Epstein-Barr virus
UICC = Union Internationale Contre le Cancer
VCA = viral capsid antigen

separately interviewed to check on the data obtained from their children. It is estimated from the latter study that more than 90% of cases of nasopharyngeal carcinoma in young Hong Kong Chinese could be attributed to consuming salted fish during childhood. In both studies the cases and controls were sex and age matched to within five years. As other more nutritious foods have become readily available and salted fish has become more expensive than chicken, the traditional habit of Hong Kong Chinese feeding their children salted fish is fast disappearing. It is tempting to suggest that the sharp progressive drop in their annual age-adjusted incidence rates during 1978 to 1981 from 41.5 per 100,000 to 25.8 for men and from 16.9 to 11.4 for women reported by the Hong Kong Cancer Registry might be related to this change of habit.

Judging from their age-specific incidence curves, the Swedes[6] and American whites and blacks[4] appear to have a different origin for nasopharyngeal carcinoma from that of Hong Kong or Singapore Chinese[8] or Chinese Americans.[4] The curves for the three groups of Chinese have a similar pattern, differing only in height. In Chinese the curves rise sharply after the third decade, whereas those for the non-Chinese groups show a rise after the fourth or fifth decade. If we consider the latency period—that is, the period between carcinogenic initiation and clinical manifestation—in nasopharyngeal carcinoma to be about 20 to 30 years, we should look for environmental initiators operating during early childhood in the case of Chinese and in the non-Chinese groups during their late teens and early adulthood. The Alaskan native population has a curve pattern resembling that for Chinese, but Tunisians have a bimodal curve, with the early peak at the second decade.

The rapid advance in cytogenetics and recombinant DNA technology has afforded us an opportunity to look for oncogenes in nasopharyngeal cancer cells. Their identification may help us to understand how normal nasopharyngeal epithelial cells may be transformed into carcinoma cells. It may also open new frontiers in the diagnosis and management of cases of nasopharyngeal carcinoma.

Diagnosis

The symptoms of nasopharyngeal carcinoma are well known. It is the unawareness of the disease in low-incidence areas that causes undue delay in its diagnosis. Moloy and colleagues remind us that serous otitis media may be a presenting manifestation of nasopharyngeal carcinoma. In places where both pulmonary tuberculosis and nasopharyngeal cancer are prevalent, blood-stained morning sputum due to coughed-up postnasal drip is often a cause of delay in diagnosis. Patients are usually investigated first for pulmonary tuberculosis and may be treated for it when they have shadows on their chest radiographs because of past infection. A delay of three to six months is not unusual in such cases. Nasopharyngeal cancer is not thought of until other symptoms and signs of it appear. Cervical lymph nodal enlargement is the most frequent first symptom. Because the cancer is painless, except in the presence of concurrent infection, it is often not noticed by a patient, especially if he or she has a fat neck, until there is a large tumor. Sometimes the primary tumor in such a case may not be found even by computed tomographic (CT) scan if it is small or flat. In the presence of a hypersensitive gag reflex, the nasopharynx may be examined by fiberoptic nasopharyngoscopy or inspected by the use of a Yankauer speculum if the tumor is suspected to be in the fossa of Rosenmüller. The speculum allows biopsy of the fossa under direct vision after topical anesthesia has been applied. If results of the nasopharyngeal biopsies are negative, any enlarged node should be removed and imprint smears made from it for staining for the nuclear antigen of Epstein-Barr virus (EBNA)[9] in the tumor cells before submitting the specimen for histopathology. If the EBNA test is positive, the primary tumor is most likely nasopharyngeal carcinoma, especially if the enlarged node is in the spinal accessory chain. The close association between nasopharyngeal carcinoma and Epstein-Barr virus allows EBV serology to be used in screening for the cancer among high-risk persons, such as first-degree relatives, especially siblings, of patients in high incidence areas.[10] An elevated serum titer of IgA to the viral capsid antigen (VCA) of 1:10 or greater may be the first indication of subclinical nasopharyngeal carcinoma. For such a case, multiple nasopharyngeal biopsy specimens are warranted even in the absence of symptoms or a demonstrable tumor, especially if the titers of other EBV-specific antibodies are also elevated. After specific treatment, EBV serology does not seem to reflect the state of the tumor burden to the same acceptable degree of reliability as before treatment. Hence it is of only limited help in following progress in individual patients. Actually, the production of antibodies to the various EBV-specific antigens is influenced by many factors other than the availability of EBV-specific antigens. In pretreatment cases of stage I nasopharyngeal carcinoma, the false-negative rate may be as high as 12% when the diagnostic titer of IgA anti-VCA is set at greater than 1:5. The false-positive rate is about 10%, which reflects the presence of other tumors.

The value of CT scan is in showing involvement of the soft tissue in the parapharyngeal retrostyloid and prestyloid spaces, the retropharyngeal space and the neck. Primary tumor extensions through the fissures and foramina at the base of the skull to the cranial cavity, the paranasal sinuses and the orbits are clearly shown by CT. However, for showing a small tumor in the nasopharynx, CT is clearly useless as are plain radiography and conventional tomography. In differentiating between cranial nerve involvement by recurrent tumor and irradiation neuropathy, and between temporal lobe irradiation encephalopathy and other nonneoplastic neurologic disorders and meningeal metastasis, CT scan is invaluable. Incidentally, genuine blood-borne metastasis has not been encountered in the brain, although it is not immune to invasion by adjacent meningeal metastasis or cranial extension of the primary tumor. For finding soft tissue involvement or an abnormality in the brain, magnetic resonance imaging is superior to CT. However, magnetic resonance imaging does not show up bones but only the marrow within them.

Staging

We have at present no universally accepted stage classification for nasopharyngeal carcinoma. This is hampering clinical research on the cancer, because no meaningful intercenter or even intracenter comparison of treatment results is possible. A good stage classification is one that gives an accurate indication of the prognosis and the extent of the disease to guide treatment planning. It must provide clear and practical definitions of the anatomic limits and criteria for the various stages. Without such a classification, no meaningful clinical trial can be mounted. Of the number of stage classifications that we have at present, the one formulated by the International Union Against Cancer (Union Internationale Contre le Cancer, UICC), and that by the American Joint Committee for Cancer Staging and End-Results Reporting (AJC) are more widely used than the others, but neither is satisfactory. In the AJC classification, the inferior limit of the nasopharynx is defined as level with the plane of the hard palate. This plane can only be observed in a lateral radiograph of the nasopharynx, however. It cuts across the lower part of the torus tubarius and the fossa of Rosenmüller to reach the posterior wall of the nasopharynx above the tubercle of the anterior arch of the atlas vertebra. To most clinicians the nasopharynx is that part of the pharynx situated above the posterior margin of the soft palate in its resting position and hidden from view through the opened mouth. This definition is much more practical and is adopted by the Ho classification.[11] In the UICC classification, the posterosuperior wall is defined as extending from the level of the junction of the hard and soft palates to the base of the skull. This definition of the lower limit of the posterior wall is vague and presumably it corresponds to the level of the lower margin of the basiocciput and the anterior margin of the foramen magnum. If so, it is about the same level as the lower limit defined in the AJC classification. In both classifications, T_1 is defined as tumor confined to one site or region, presumably one wall, and T_2 to two sites or regions. The limits of the primary tumor within the nasopharynx are not easy to ascertain, even for an expert. Furthermore, a carcinoma may occur submucosally and not be readily visible. The diagnosis in such a case is established by biopsy. Submucosal infiltration may occur at some distance from the macroscopic tumor. The fossa of Rosenmüller is in fact astride both the lateral and posterior walls and it is a common site of origin of the primary tumor. Consequently, a small tumor there may be reckoned to have involved two sites. It is therefore suggested that T_1 and T_2 should be combined as T_1, as in the Ho classification. From the point of view of correlating with the prognosis, the T_3 in both the UICC and AJC classifications could well be downstaged to T_2; T_4 with tumor involvement of bones below the actual base of the skull downstaged to T_3 and the rest, such as involvement of the actual base of the skull and cranial nerves at or above it, to remain as T_4. In this respect involvement of cranial nerves at the retrostyloid space should be considered T_4 involvement because the upper limit of the space is the jugular foramen at the base of the skull. Involvement of the hypopharynx should also be staged T_4 because it carries a very poor prognosis. The nodal staging in the UICC classification is designed primarily as a guide for surgical treatment by block dissection, whereas radiation therapy is the primary treatment of choice not only for the primary tumor in cases of nasopharyngeal carcinoma but also cervical nodal metastases. They are staged by UICC according to the laterality of the involvement and mobility of the involved nodes. Because the nasopharynx is a midline organ with bilateral lymphatic drainage, the cervical nodes should always be treated on both sides and according to the level of involvement, which corresponds better with the prognosis than laterality or mobility of the nodal involvement.[12]

The AJC classification included a measurement of the diameter of the involved nodes, with a diameter of between 2.9 and 3.0 cm as the cut-off point between N_1 and N_2 and between 5.9 and 6.0 cm as that between N_2 and N_3. Measurements of the diameters of cervical nodes, especially the deep-seated ones, are most of the time estimated subjectively. They are hence very inaccurate. It is easier to see and feel whether the lower poles of the enlarged nodes have extended below the neck crease at or just below the thyroid notch. The crease is taken arbitrarily to be the boundary between N_1 and N_2 regions in the Ho classification.

Treatment

The treatment results should be better now that we have the CT scanner to help us detect previously undetected soft tissue involvement to reduce geographic miss. With the availability of the computerized radiotherapy planner, a better dose distribution in the target volume is expected with reduction of dose to normal vital organs such as the brain stem and spinal cord and important organs such as the eyes. Radiosensitizers and radioprotectors are still in the development stage, and hyperbaric oxygen is a disappointment. Prophylactic irradiation of apparently uninvolved cervical lymph nodes has been shown to be unnecessary if a patient can attend regularly for follow-up.[5,12] Chemotherapy has only limited success in treating visceral metastasis, with a response rate of about 30% with the various agents that have been tried. Primary tumor and bone metastases appear to be almost unresponsive. Although distant metastasis presents a problem, the predominant site of metastasis is in bone where it is most resistant to chemotherapeutic agents. The control of the primary tumor is not just a matter of increasing the irradiation dose. There is a limit, around a time and dose fractionation factor of 108—that is, around 6,600 cGy (centiGray) over six weeks—beyond which the tumor control curve tends to level off and the morbidity curve rises sharply. As the superior margin of the treatment field is above the sella turcica and covers the sphenoid sinus, a potential site of tumor spread, part of both temporal lobes and the pituitary-hypothalamus axis would be within the target volume. In long-term survivors we are seeing complications arising from the heavy irradiation of these parts. Irradiation myelopathy is now rarely encountered because of good shielding of the spinal cord by using an anterior cervical field with a median spinal cord shield and accuracy of beam direction by the use of a transparent Perspex shell specially made for patients to wear to facilitate setting up.

Control of the primary tumor needs further research. Even in stage I cases there is a five-year cumulative primary tumor recurrence rate of 21%.[13] The overall five-year actuarial survival rate for stages I through IV cases is about 45%, and the relapse-free survival rate after initial treatment is 33%. In stage I cases, the corresponding rates are 80% and 63%.

Patients with primary tumor recurrence often benefit from a second course of radiotherapy, but the rate of late complications such as temporal lobe, brain-stem and cranial nerve (most commonly the 12th, 5th and 6th) irradiation neuropathy, temporomandibular joint capsular fibrosis and perceptive deafness would be higher. By proper shielding of a large part of the oral tongue and minor salivary glands, dryness of the mouth can be minimized. By attention to oral hygiene and the use of fluoride gel, less irradiation dental caries is expected. Prevention is better than cure and for nasopharyngeal carcinoma, prevention is probably not a too-distant possibility.

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Clinicopathologic Conference

A Cystic Lesion in a 55-Year-Old Man

Discussants

JIM AMERIAN, MD; IAN RENNER, MD; WILLIAM BOSWELL, MD, *and* TELFER REYNOLDS, MD

An edited transcript of Medical Grand Rounds held at the Department of Medicine, Los Angeles County-University of Southern California School of Medicine, Los Angeles, on March 14, 1984. David A. Goldstein, MD, Associate Professor of Medicine, was the coordinator and editor of this conference.

JIM AMERIAN, MD:* The patient, a 55-year-old man, was admitted after having sharp, midepigastric abdominal pain, radiating through to the back, for six days. He also had nausea and vomiting associated with some diarrhea but said he had no recent fever or chills. The patient stated that he had had a 7-kg (15-lb) weight loss during the previous three months. His appetite had been poor for about a year. He had no history of biliary disease, peptic ulcer disease, jaundice or abdominal trauma.

The medical history included three hospital admissions for episodes of alcoholic pancreatitis, the last episode six months before this admission. He said he had not traveled recently but related 15 pack-years of smoking and an intake of a quart of whiskey per week all his adult life. The patient listed his medications as cathartics and antacids (milk of magnesia and Maalox) taken occasionally and vitamins daily.

On physical examination he was well developed, thin and appeared to be in moderate distress His blood pressure was 140/80 mm of mercury, pulse 96 per minute, respiratory rate 14 per minute and temperature 37°C (99.0°F). There were no orthostatic changes. There was no scleral icterus. On examination of the abdomen there were midepigastric fullness, generalized abdominal tenderness maximal in the midepigastric area and normal bowel sounds. The liver and spleen were not palpable and no ascites was detected. There was a slight decrease in skin turgor but no spider angiomata and no palmar erythema. A stool specimen was negative for occult blood. The patient was oriented to person and place only.

Laboratory studies disclosed the following values: sodium, 141, potassium, 3.1, chloride, 103, and bicarbonate, 27 mEq per liter; calcium, 8.7, phosphorus, 1.7, glucose, 132, urea nitrogen, 10, uric acid, 5.1, and creatinine, 1.0 mg per dl; alkaline phosphatase, 179 IU per liter; total protein, 6.4, and albumin, 3.2 grams per dl; total bilirubin, 0.8, and direct bilirubin, 0.1 mg per dl; serum aspartate aminotransferase (glutamic-oxaloacetic transaminase), 15, and serum alanine aminotransferase (glutamic-pyruvic transaminase), 26 units per liter. The leukocyte count was 11,100 per μl (94% segmented neutrophils), platelets were 141,000 per μl and hematocrit, 33.9%. Serum amylase was 154 (normal, 75 to 140) and urine amylase 1,518 units per liter (normal, less than 500).

Hospital Course

The patient was diagnosed as having pancreatitis and was treated with meperidine hydrochloride (Demerol) and hydroxyzine hydrochloride (Vistaril) given intramuscularly, fluids given intravenously, thiamine, multivitamins and folate. On the second hospital day, he went into alcohol withdrawal. He was treated with oral administration of lorazepam. On the fourth hospital day, a fever of 39°C (102.2°F) developed. At this time, he had no abdominal pain.

On the sixth hospital day, his maximum temperature by mouth was 38°C (101°F). The leukocyte count was elevated at 18,400 per μl with a differential of 82% segmented forms, 7% bands, 5% lymphocytes and 6% monocytes. By the eighth hospital day, the patient was afebrile. Blood cultures were negative. The serum amylase level was 199 units per dl, urine amylase 354 units per dl and the leukocyte count was 15,300 per μl, with a differential of 89% segmented cells, 1% bands, 4% lymphocytes and 6% monocytes. On the ninth hospital day, an ultrasound study and a computed tomogram of the abdomen were obtained. Serum amebic titers were less than 1:32. On the 11th hospital day, a procedure was done.

Dr Renner, would you discuss your approach to this case and provide us your final diagnosis?

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(Amerian J, Renner I, Boswell W, et al: A cystic lesion in a 55-year-old man—USC School of Medicine, Los Angeles [Clinicopathologic Conference]. West J Med 1985 Jul; 143:74-79)

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Differential Diagnoses

IAN RENNER, MD:* There are several ways to approach a case presented at these exercises. My preference is to discuss the differential diagnosis as the case presents and then to confirm or delete possibilities as the course of the illness unfolds.

Ideally, the list of diagnostic possibilities should be few; the aim of any good clinician should be to focus on the most likely diagnoses and to proceed in a logical and cost-effective manner to exclude or confirm his or her diagnostic impressions. I hold no brief for a long differential diagnosis, especially where little thought is given to ranking the likelihood of such diagnoses.

We already know from the title of this conference that a cystic lesion is present in the liver; however, only a physician gifted with precognition could have predicted its presence before the radiologic investigation. This aspect of the case will, therefore, be discussed at the appropriate time.

Our patient presented with a six-day history of symptoms characteristic of alcohol-associated chronic relapsing pancreatitis. The name itself is unfortunate and inaccurate in that it implies the absence of any acute process; I prefer the term acute-on-chronic pancreatitis. The triad of nausea, vomiting and epigastric pain radiating through to the back is usually present in such cases and is almost invariably associated with prolonged heavy drinking.

The weight loss and long-standing poor appetite are almost certainly due to chronic alcoholism and not to pancreatic insufficiency, because in the latter case enhancement of appetite is the rule, even where there is massive weight loss.

The physical findings on admission of epigastric fullness and tenderness in the presence of normal bowel sounds should at the outset suggest the possibility of a common complication of this illness, namely, a pancreatic pseudocyst. Physical examination will disclose an abdominal mass in only 50% of these patients, even though a large cyst may be present.[1]

The laboratory abnormalities include a moderately elevated serum alkaline phosphatase level at 179 IU per dl, serum albumin content depressed at 3.2 grams per dl, a decreased hemoglobin at 11.4 grams per dl, mild elevation of the leukocyte count without any left shift, an elevated mean corpuscular volume of 100 cu microns, a serum amylase level of 154 units per dl and a urine amylase value of 1,518 units per dl.

In the presence of normal transferases I would be inclined to attribute the elevated serum alkaline phosphatase value to a complication of chronic pancreatitis, namely, periductular sclerosis involving the distal common bile duct as it passes through the head of the pancreas. The low serum albumin level is consistent with levels usually observed in such patients due to poor nutrition. The anemia and moderate macrocytosis probably reflect the moderate bone marrow suppression and folate deficiency commonly seen in such cases. Marginal elevation of the serum amylase level with moderate elevation of the urine amylase content is common in this type of pancreatitis[2-4] and merely reflects the ability of the kidneys and the reticuloendothelial system to efficiently clear any modest increase in the release of amylase from the pancreas.

It is important to remember that chronic relapsing pancreatitis is lobular in distribution and does not involve the pancreas globally as is the case with acute pancreatitis. Thus, the biochemical disturbances, especially the elevation of serum amylase or lipase, may be only marginal.

At this point, I suggest that we are dealing with the following diagnostic problems:

1. Chronic alcoholism.
2. Chronic relapsing pancreatitis.
3. Probable pancreatic pseudocyst.
4. Possible periductal stenosis of the distal common bile duct due to pancreatic fibrosis.

Four days after admission to hospital and ten days after the onset of pain, a fever of 38°C developed, followed by an elevated leukocyte count of 18,400 per μl with some evidence of a left shift.

Blood cultures were done and failed to grow any organisms. No antibiotics were given at this time. In this setting, the possibility of my hypothetical pseudocyst converting to a pancreatic abscess must be considered, as fever is unusual in cases of uninfected pseudocyst.[1]

The characteristic features of a pancreatic abscess are fever, leukocytosis of greater than 18,000 per μl in a patient recovering from an attack of acute pancreatitis or, in this case, of chronic relapsing pancreatitis.[1] Our patient at this time thus fulfills all of the above criteria for possible pancreatic abscess formation.

In the 1970s and before the development of sophisticated modalities such as ultrasound and computed tomographic (CT) scans, a plain abdominal film to look for evidence of pancreatic calcification, displacement of any gas-filled viscus and the "soap bubble" pattern characteristic of retroperitoneal sepsis would have been mandatory. In addition, an upper gastrointestinal series would have been carried out to more clearly identify any space-occupying lesion compressing the stomach or duodenum. It is still essential to get plain abdominal and chest x-ray films in all such cases, especially as a pleural effusion will be present in 20% to 35% of patients who have a pseudocyst.[5]

What is surprising to me is the five-day delay in doing an abdominal ultrasound study after the patient had a fever spike of 39°C on the fourth hospital day. I have looked up the date the procedure was done, thinking that the onset of fever must have occurred on a weekend when radiologists are usually found basking in the sunshine; this was so. On the sixth day of his hospital course, however, the patient was still febrile with a leukocyte count of 18,400 per μl. By this time, at least, an ultrasound study should have been done. Blood specimens were obtained for culture, which failed to grow any organisms, and no antibiotics were given. On the ninth hospital day and 15 days after the onset of pain, nausea and vomiting, the long-awaited ultrasound study was carried out. The following day, a CT scan of the abdomen was done and on the 11th hospital day, he had a "procedure."

Dr Boswell, will you describe the ultrasonographic and CT scan findings, please?

Radiologic Findings

WILLIAM BOSWELL, MD:* Thank you, Dr Renner. As radiologists, it is our job to look beyond the obvious findings on a film and assist specialists and subspecialists in solving a diag-

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nostic dilemma. Looking beyond the obvious, I found that although the fifth hospital day occurred on a weekend, it was cloudy during this entire period and even a radiologist could not be found basking in the sun. Let us now review the patient's x-ray findings.

A chest x-ray film was taken at the time of admission and was normal. No evidence of pleural effusions, areas of atelectasis or infiltrates were seen. An ultrasound study of the pancreas was done on the ninth hospital day. The gallbladder was contracted and poorly seen, presumably because the patient had eaten recently. The common bile duct was visualized and measured 7 to 8 mm in diameter, the upper limits of normal. The pancreas was relatively normal in size but displayed decreased echogenicity consistent with pancreatitis. No specific fluid collections were noted in the region of the pancreatic bed.

An 8.1 by 4.1 by 7.8 cm hypoechoic lesion was identified cephalad and anterior to the pancreas, possibly involving the left lobe of the liver (Figure 1). The interface between the lesion and the liver was irregular. The lesion itself appears to be surrounded on three sides by liver parenchyma. There was a sharply marginated back wall to the lesion with good through-transmission, suggesting primarily a fluidlike collection. Some echoes were noted within the lesion, possibly representing debris. The stomach was noted to be lateral to the lesion.

On the tenth hospital day, a CT scan of the abdomen was done. Orally administered contrast material outlines the stomach and gastrointestinal tract. A well-circumscribed lesion is seen in the region of the left lobe of the liver (Figure 2), surrounded almost entirely by liver parenchyma except on its inferior aspect. The CT scan numbers are in the range of 10 to 20, slightly higher than is expected for a water-dense material. Within this collection, there is some material that is slightly higher in density. This could represent blood or debris within the fluid. The pancreas is enlarged with a low-density region seen centrally, suggesting a dilated pancreatic duct (Figure 3). A second fluidlike collection is seen in the lesser sac lateral and superior to the pancreatic tail (Figure 2). The inferior aspect of the anterior lesion, which appears to involve the left lobe of the liver, is located just anterior to the superior aspect of the pancreas. This corresponds to the findings of the pancreatic ultrasound study. The CT scan of the abdomen shows no other abnormalities.

DR RENNER: Several questions come to mind:

1. How accurate is ultrasound in detecting dilated extrahepatic ducts?

2. Can we be certain that there were no stones in the gallbladder or in the common bile duct?

3. Do you feel that the CT scan shows evidence of calcium deposits in the pancreas?

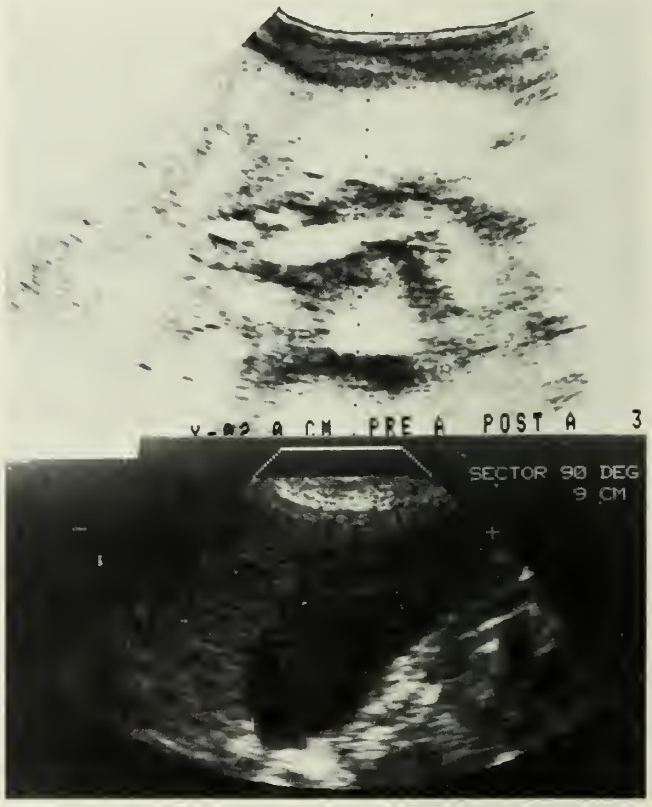

Figure 1.—Transverse and longitudinal ultrasound scans of the upper abdomen. A large, relatively hypoechoic fluidlike lesion is shown anterior and cephalad to the pancreas.

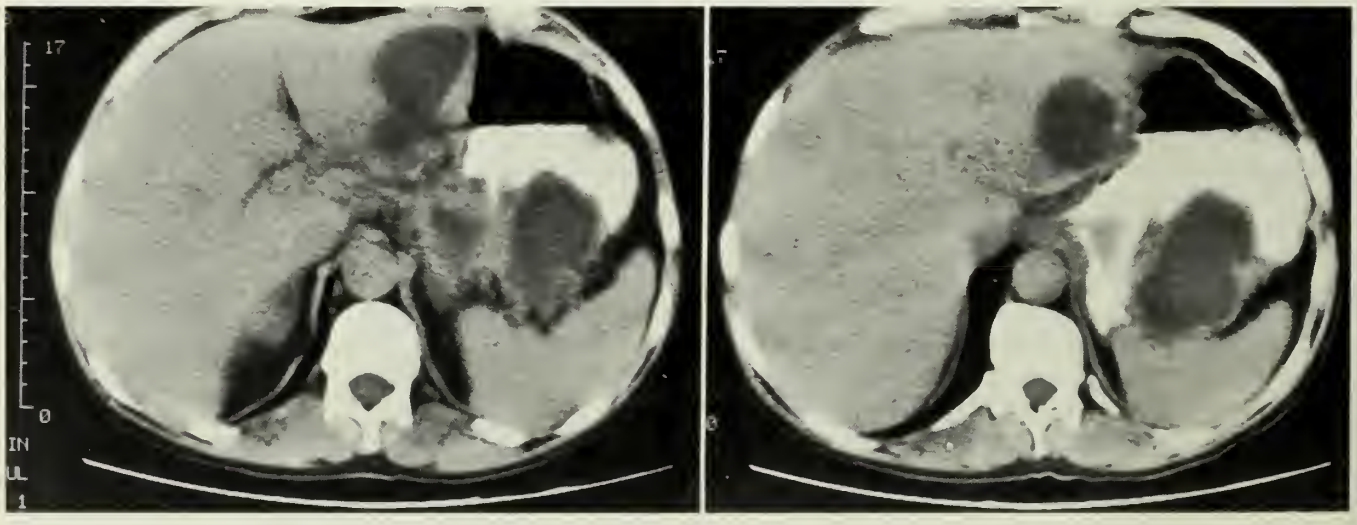

Figure 2.—Computed tomographic scans through the upper abdomen show anteriorly the fluid collection within the left lobe of the liver. Additionally, a fluid collection is seen in the lesser sac posterior to the stomach.

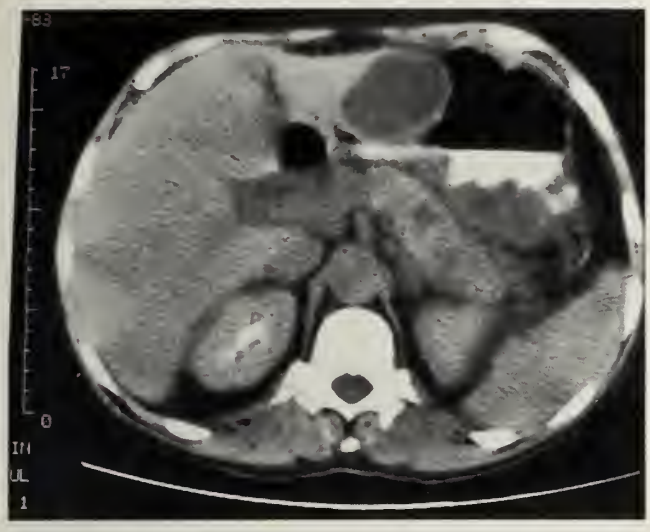

Figure 3.—A computed tomographic section through the pancreas shows a mildly enlarged tail of the pancreas in which a somewhat linear low-density area is identified, believed to be a dilated pancreatic duct. Additionally, the lower limits of the fluid collection in the left lobe of the liver are identified anteriorly. Some slightly higher density material is seen near the bottom of this lesion. The lower limits of the lesser fluid collection are also seen posterior to the stomach and anterior and lateral to the tail of the pancreas.

4. Does the failure to show any communication between the hepatic cyst and the extrapancreatic pseudocyst on the CT scan rule out their possible intercommunication?

5. Can you reliably differentiate abscess from a simple pseudocyst?

DR BOSWELL: Ultrasound is extremely accurate in assessing the diameter of the extrahepatic biliary ducts. Depending on the specific measurement used for the cross-sectional diameter of the duct, its accuracy increases or decreases. At our institution, we use 8 mm as the upper limit for a normal-sized main bile duct. A diagnostic accuracy of greater than 95% would be anticipated using 8 mm as the maximum diameter of the duct. With regard to your second question, when the gallbladder is well distended, an accurate examination should detect virtually all stones. In evaluating technically adequate scans at this institution, only 2 cases out of about 300 to 400 showed no gallstones at an operation when gallstones were reported to be evident on the ultrasound examinations. One patient had almost certainly passed a stone between the time the scan had been done and the operation. With the other patient, we do not have a specific answer for the discrepant findings. In evaluating the common bile duct for the presence of gallstones, our accuracy is much lower. In a large series at this institution, about 25% of common bile duct stones were visualized by ultrasound study. The remaining 75% were not seen for various technical reasons, usually due to incomplete visualization of the entire common bile duct.

This particular CT scan does not show any evidence of calcium deposits within the pancreas. CT scans, because of their remarkable ability to discriminate different tissues, are ideal for detecting calcium deposits within the pancreas.

The answer to your fourth question regarding the communication between the hepatic cyst and the extrapancreatic pseudocyst is easy. As the sections from CT scans are axial and not always in the plane of the different collections, it is not unexpected that a communication would be found. In cases such as these, when a communication is shown, it is more often serendipitous than expected. One might, however, demonstrate a communication between the two cysts using the skinny-needle technique by instilling contrast in one cyst and showing that contrast material flows to the second cyst.

Differentiating abscess from a simple pseudocyst may, on occasions, be simple but is more often difficult. Specific findings of debris and gas within a lesion would certainly point one toward the possibility of an abscess. A simple pseudocyst would be expected to have a well-circumscribed wall and fluid-dense material within it that is homogeneous. The most reliable way to differentiate between abscess and a simple pseudocyst is to aspirate the lesion with a 22-gauge skinny needle and examine the fluid obtained.

DR RENNER: The intriguing findings shown by both ultrasonography and CT scan do not change my initial diagnosis of pseudocyst formation due to acute-on-chronic pancreatitis with almost certain main pancreatic duct stricture and consequent ductal rupture. The diagnosis of pancreatic pseudocyst by ultrasound and CT scan is usually straightforward and is established by imaging an encapsulated cystic collection that forms as a consequence of release of proteolytic enzymes from a ruptured pancreatic duct. Pseudocysts have the striking ability to erode into the retroperitoneal space and then to appear in unusual and remote locations including even the mediastinum and the pelvis.[6,7]

Thus, renal disease may be simulated by a dissecting pseudocyst, which usually involves the left kidney,[8] whereas the lienorenal ligament provides a natural pathway for proteolytic enzymes to the splenic hilum with direct involvement of the spleen.[9] The liver, however, has no such convenient pathway for free enzymes to travel; hence, it is surprising and very uncommon for hepatic parenchyma to be involved. During the past two years, however, we have seen at the Los Angeles County-University of Southern California Medical Center two very unusual cases of solitary pseudocysts in the liver (following acute pancreatitis) shown by CT scan. In one case, no evidence of pancreatic communication was seen and the diagnosis was clinched by finding cyst fluid serum amylase levels exceeding 18,000 units per dl using the skinny-needle aspiration techniques under CT scan guidance.

The body and tail of the pancreas showed obvious enlargement with an ill-defined, irregularly dilated ductal system on the CT films. This finding is the obvious setting for ductal rupture and pseudocyst formation. I am reluctant to concede the possibility of two pathologic diagnoses in this case and, therefore, feel that the cystic lesion in the liver is, in fact, a pseudocyst. It is entirely possible, however, that the two lesions are dissociated and one must consider the differential diagnosis of cystic lesions in the liver. In brief, these include amebic abscess—an unlikely diagnosis with a titer of 1:32—and a solitary cyst of the liver, which cannot be ruled out, nor can unusual presentations of hydatid cyst, hematomas or the rare cystadenoma. None of these suggestions sway me from my initial diagnosis.

Coming back to the other abnormality observed by ultrasonography—the dilated common bile duct—again, I would be inclined in the presence of known chronic pancreatitis to stick to my original diagnosis, that the dilation is due to

periductal sclerosis. The elevated serum alkaline phosphatase level thus could be due to this lesion or to the presence of the cystic liver lesion (or to both).

The diagnostic procedure of choice, and the one that was probably carried out in this case, was skinny-needle aspiration of both cystic lesions under CT scan guidance. If I have guessed correctly, we should obtain reddish fluid from both cysts, the contents of which should show high amylase levels and an elevated leukocyte count without growth of organisms on culture.[10,11] This type of approach has the advantage of allowing us to exclude abscess formation and, according to numerous recent reports,[10-12] may be a way of determining whether a cyst will resolve spontaneously or ultimately require a surgical procedure, by observing how quickly the fluid reaccumulates.[12]

It is quite conceivable that the pseudocyst adjacent to the pancreas has become infected; this would be an unusual development, however, in view of the resolution of the patient's fever without the use of any antibiotic therapy.

Dr Renner's Clinical Diagnosis

1. Antecedent chronic alcoholism.
2. Chronic relapsing pancreatitis.
3. Peripancreatic pseudocysts.
4. Hepatic pseudocyst.
5. Probable periductular distal common bile stenosis due to pancreatic fibrosis.

DR AMERIAN: On the 11th hospital day, the cystic liver lesion was aspirated under the guidance of ultrasound; about 10 ml of foul-smelling, yellow, cloudy fluid was obtained. Cultures from this material grew 2+ *α-Streptococcus* (not group D), 2+ *Escherichia coli*, 2+ *Fusobacterium* and 2+ Gram-positive anaerobic cocci. The amylase value was 4,268 units per dl. The patient was initially treated with clindamycin phosphate and gentamicin sulfate. This antibiotic regimen was subsequently switched to cefotaxime sodium and metronidazole. He received this regimen for ten days in hospital and was then discharged home and instructed to take oral ampicillin and metronidazole for an additional ten days. At the time of discharge, his leukocyte count was 9,900 per μl with the following differential: 68% segmented neutrophils, 23% lymphocytes, 6% monocytes and 3% basophils. Except for fever on the fourth to the sixth hospital days, the patient remained afebrile with no abdominal pain.

Dr Reynolds, could you briefly discuss the management of this case?

Management

TELFER REYNOLDS, MD:* The Liver Service physicians saw this patient in consultation soon after discovery of the hepatic mass lesion. Our analysis of his illness was very similar to Dr Renner's. To the list of hepatic lesions with a relatively low CT scan density and reduced sonographic echoes, I would add malignancy, both primary and secondary. At times, neoplasms have such a uniform consistency that they give fewer sonographic echoes than does normal liver. In this patient, we thought the most likely lesion was an intrahepatic pseudocyst of the pancreas. Frankly, I would not have considered this a possibility before 18 months ago, when we saw a similar case with a 6-cm pancreatic pseudocyst that proved to be partially imbedded in the posterior aspect of the left lobe of the liver. This must not be excessively rare as the recent literature contains several reports of similar cases.[13-17] For this patient, we advised needle aspiration of the intrahepatic mass to confirm its cystic nature and to obtain an amylase level of the contents. The evidence of infected fluid was a total surprise to all of us involved with the case because fever had subsided and there were virtually no residual symptoms. The second cyst was not aspirated as it seemed certain that it was a pancreatic collection and treatment would likely be unchanged whether or not it was infected. At this point, the patient was presented at a combined medical-surgical conference and, after considerable discussion, we elected to treat him for ten days with intravenous administration of antibiotics and then to reevaluate. Several of the physicians attending the conference were skeptical of this approach and felt strongly that he should have an immediate operation for external drainage of the presumed "pancreatic abscess." Certainly most textbooks and articles on pancreatic abscess mandate surgical drainage. It was largely because of this patient's paucity of symptoms and lack of systemic evidence of sepsis that medical therapy was elected.

In a somewhat analogous lesion, pyogenic liver abscess, surgical drainage has until recently been considered absolutely essential for survival. In 1953, McFadzean and colleagues from Hong Kong reported the cases of 14 patients with pyogenic liver abscess who survived with needle drainage and antibiotics.[18] This report was largely ignored. In 1979, however, we reported the recovery of six patients who did not have surgical drainage[19] and soon after this an additional ten patients at the Kaiser Hospital in Los Angeles were reported to recover with medical treatment.[20] Our current experience is that surgical drainage is rarely needed for pyogenic liver abscess; even needle aspiration may be unnecessary if an organism has been identified in blood cultures.[21]

It is too soon to say whether a similar change in the approach to treatment of other intra-abdominal abscesses will occur. The liver is a highly vascular organ and there is no fibrotic capsule around a liver abscess so that antibiotic penetration can be expected. An infected pancreatic pseudocyst may be another matter, however, because there is a fibrous capsule and no surrounding vascularized tissue. Nevertheless, Gerzof and co-workers recently reported successfully treating 24 patients with intra-abdominal abscesses by percutaneously placed drainage catheters and parenteral antibiotics.[22] Four of these patients had infected pancreatic pseudocysts or phlegmons and three of them recovered without surgical drainage. I think it is too soon to advocate a trial of medical treatment of cases of pancreatic abscess without continuous drainage of some sort, either surgically or by a percutaneously placed catheter. It is entirely possible, however, that this sort of treatment could be successful in some patients, so perhaps it should be tried in those who are not critically ill.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Cranial Electrotherapy Stimulation

QUESTION:

Is the use of cranial electrotherapy stimulation considered accepted medical practice or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on General and Family Practice, Internal Medicine, Neurology and Psychiatry, cranial electrotherapy stimulation is considered investigational. This noninvasive procedure involves the application of small pulses of electric current to the patient by means of electrodes placed behind the ears. It is intended to control stress-related disorders such as anxiety, depression, insomnia and various chemical dependencies.

The scientific studies supporting the efficacy of this technique are not convincing. Few of these studies are double-blind and they fail to cite the diagnostic criteria for the disorders evaluated or adverse reactions. There is no reasonable or consistent body of information available to suggest other than placebo effects from this type of treatment.

Controlled clinical trials with larger numbers of patients conducted by experienced investigators are required before cranial electrotherapy stimulation can be considered accepted practice.

Diagnosis and Management of Lower Gastrointestinal Tract Hemorrhage

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Our topic for this conference is "Diagnosis and Management of Lower Gastrointestinal Tract Hemorrhage" and John P. Cello, MD, will give this presentation. Dr Cello is Chief of Gastroenterology at San Francisco General Hospital and an Associate Professor of Medicine.*

Historical Background

DR CELLO:† The colon and its diseases played a central role in ancient Egyptian medicine. All vessels, including those carrying blood, mucus, urine, semen, water and air, were believed by the ancient Egyptians to come from the heart, but they were felt to have a second assembly center around the rectum. Blood, it was believed by the Egyptians, could become flooded with *ukedu* or feces and carried throughout the body. They were so concerned about this dangerous material that ritual purges and enemas played an essential role, both during life and after death, for the Egyptians. During the next 2,000 years of western civilization, healers were preoccupied with the importance of colonic function, so much so that our principal title of "physician" is derived from "one who administers physic"—that is, enemas and laxatives.

Differentiating Upper From Lower Gastrointestinal Tract Bleeding

The most alarming of colonic dysfunction symptoms experienced by patients is the passage of bright red blood per rectum. I will review some of the most recent advances in our approach, both diagnostically and therapeutically, to patients with significant hematochezia.

It would seem very easy to differentiate upper from lower gastrointestinal tract hemorrhage, and it is so in most patients. One can be certain that if a patient has hematemesis or melanemesis (coffee-grounds emesis), blood is passing into the gastrointestinal tract from a site proximal to the ligament of Treitz. In most instances, this bleeding is from esophagus, stomach or duodenum. Recall, however, that nasopharyngeal, tracheobronchial or pancreaticobiliary systems likewise drain into the proximal gastrointestinal tract and on occasion these may be the sites of hemorrhage. Bleeding from these sites may be manifested by hematemesis and melanemesis. The companion to hematemesis and melanemesis usually indicating a source of bleeding in the proximal gastrointestinal tract is melena, the passage of dark liquid, black, tarry, foul-smelling stools. In some instances, however, melenic stools are actually from cecal bleeding with slow intestinal transit. What about hematochezia, bright red blood per rectum? In most instances it signifies bleeding from the distal bowel, particularly the distal small bowel or the colon. However, in about 10% to 15% of patients with vigorous hematochezia, the bleeding lesion is actually from the proximal gastrointestinal tract. The most common lesion of the upper gastrointestinal tract associated with hematochezia is brisk arterial bleeding from an ulcer crater, particularly a posterior duodenal bulbar ulcer penetrating into the gastroduodenal artery. On occasion also, hematochezia can be from an aortoduodenal fistula or even from infarction of the small bowel with ileus.

Lower gastrointestinal tract bleeding is not a disease entity in itself, but is really a manifestation of a wide array of diseases that present clinically as hematochezia. The largest series to date in which the etiology of hematochezia was reviewed was by Tedesco and co-workers from Emory University in Atlanta; the series comprised 258 patients with no abnormalities found on proctoscopy (Table 1).[1] The patients were admitted to hospital, given transfusions and then, as their first diagnostic procedure, had a single-contrast barium enema followed within three to four days by an elective colonoscopy. With this approach, a third of the patients had no lesion detected. Thus, a third of these patients who were admitted to hospital with hematochezia had no colonic source for the hematochezia identified. Amost 19% had colonic diverticula alone so that in their series, diverticular bleeding was the most common identifiable cause of hematochezia. There is, however, nothing unique colonoscopically or on barium radiography to tell which particular diverticulum is actually bleeding; in fact, the only potential source for the hematochezia was diverticula noted on barium radiography

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TABLE 1.—*Causes of Rectal Bleeding in 258 Patients With Normal Findings on Sigmoidoscopy**

Lesion	Patients	
	Number	Percentage
Diverticula	48	18.6
Polyps, >5 mm	39	15.1
Cancer	29	11.2
Inflammatory bowel disease	19	7.4
Polyps, <5 mm	18	7.0
Angiodysplasia	17	6.6
Ischemia	2	0.1
Irradiation colitis	1	0.1
Bleeding ileocecal valve	1	0.1
Incomplete	2	0.1
No lesion detected	82	31.8

*From Tedesco et al.[1]

and colonoscopy. The diverticula were followed in terms of decreasing frequency as a source of hematochezia by large polyps, cancer, inflammatory bowel disease, diminutive polyps and angiodysplasia. These figures have changed somewhat, as we now take a different approach to the evaluation of patients with hematochezia and no abnormalities found on proctoscopy.

Diagnostic Procedures

Proctoscopy

The most important diagnostic procedure to do in patients who have hematochezia is the examination of the rectum. This must be the initial diagnostic procedure and it is usually carried out by rigid proctoscopy. One of the major difficulties that medical trainees have in doing a proctoscopy on patients with hematochezia is with misinterpreting the source of the blood coming from above the depth of instrument insertion. With brisk bleeding from a distal colonic site, retrograde passage of blood into the more proximal colon is not uncommon. In fact, blood from an anorectal lesion may flow as far proximally as the ascending colon. In doing a rigid proctoscopy with the patient in the knee-chest position, no distal lesion may be noted because of the overlying blood or debris, and an examiner may misinterpret the presence of blood from above the depth of tube insertion as representing bleeding from above that depth. It is thus extremely important to examine for hemorrhoids or rectal tears because, especially in hemodynamically trivial hematochezia, distal rectal disease is the most common cause of bleeding.

There has been a dramatic shift over the past ten years in the approach to rigid proctoscopy in most American medical training programs. Before the late 1970s, a rigid proctoscopy was routinely done on initial patient contact by the primary health care provider. It was done by students, house officers, outpatient care physicians, on the wards, in a patient's bedroom and in clinics without any special procedures or special equipment. As a consequence, nearly all health care providers, regardless of their subspecialty, were proficient in doing rigid proctosigmoidoscopic examinations. More recently in the United States there has been a shift, with proctoscopy now considered virtually a "subspecialty" diagnostic procedure. It is, therefore, being done electively in endoscopy suites by specialty physicians and fellows. As a consequence, few, if any, primary health care providers have developed or retained the skills of rigid proctoscopy. There are many reasons for this. There is the general trend towards specialization that has put every invasive diagnostic procedure into a subspecialty categorization. Health care administrators are also to blame for much of this, because the facilities on wards and in clinics for carrying out proctosigmoidoscopic examinations have been extremely poorly equipped and maintained. Proctoscopy, of course, can be a messy procedure, involves the primary physician's care and attention and it provides qualitative, nonquantifiable information. Thus, house staff and attending physicians alike tend to devolve this diagnostic procedure onto other physicians, some of whom are more than willing to accept the challenge—in exchange for an increased fee generation—using flexible fiberoptic instruments. However, I think there has been a lack of discipline by supervising physicians in not insisting that this routine extension of the physical examination be done in patients who are admitted to hospital with hematochezia.

Rigid proctoscopy is *not* a subspecialty diagnostic procedure. It has advanced considerably, with major advances in the development of plastic disposable obturators and insertion tubes that cost only $5. The illumination equipment costs about $150, so there is really no excuse for not doing this examination at the time of initial patient contact. With the routine 20-cm depth of insertion, the entire rectum and the distal 5 to 10 cm of the sigmoid colon can be examined, specifically looking for anorectal tears or hemorrhoids. If a primary physician misses the opportunity to locate vigorous bleeding from a hemorrhoid, the patient may be subjected to an additional series of unnecessary, invasive, expensive and possibly dangerous diagnostic procedures. The time to make the diagnosis of hemorrhoidal or traumatic rectal bleeding or to exclude distal bleeding is during the initial contact with a patient.

Fiberoptic Sigmoidoscopy

Flexible fiberoptic sigmoidoscopy has recently been available using equipment costing more than $2,000. The most popular models are those in the range of 35 to 60 cm in length. With flexible fiberoptics, the examination can be done with the patient in the left decubitus position. Thus, there is enhanced patient tolerance of the procedure, which ordinarily does not require any intravenously given sedation. Probably the main reason for the development of flexible sigmoidoscopic equipment is the disproportionate number of cases of colorectal malignant tumors in western societies that are found in the distal bowel. Nearly two thirds of colorectal cancers are within easy reach of the 60-cm flexible sigmoidoscope. We must remember, however, that 50% of colorectal neoplasms are within easy reach of the 20-cm examination done with the rigid proctoscope. The depth of insertion achieved by most examiners with the rigid proctoscope is about 20 cm; examination with a flexible 60-cm sigmoidoscope will usually advance to about 50 cm. One will indeed pick up a larger percentage of polypoid and sessile colonic neoplasms using the longer flexible instruments. The problem with the flexible sigmoidoscopic examination is that the initial start-up costs are about 50 times greater than those for rigid sigmoidoscopy and the fees charged are often two or three times those for rigid proctoscopy.

Barium Radiography

Let us now consider barium enema radiography. This procedure has been the standard diagnostic evaluation following proctoscopy in patients with hematochezia. This examination, however, is extremely difficult to do adequately in a patient who is having vigorous bleeding. In general, barium enema evaluation should *never* be used as an early diagnostic procedure in a patient who is vigorously bleeding. The presence of blood, mucus and stool in the colon prevents adequate mucosal coating with barium. Many of the lesions, in addition, are superficial mucosal (angiodysplasia or small polyps) and would not be detected even by the finest of barium enema examinations done in a meticulously cleaned colon. Probably the main reason for avoiding barium radiography in a patient who appears to be bleeding briskly is that the use of barium limits the ability to carry out subsequent angiographic contrast studies if necessary. There have, however, been dramatic advances in the contrast enema technique, particularly with the availability of air-contrast or double-contrast studies. This procedure is acceptable in patients with chronic, intermittent lower gastrointestinal tract bleeding after proctosigmoidoscopy has been done. It is important to stress that the standard of care around the world dictates that patients undergo barium enema evaluation only *after* thorough proctoscopic examination. It is unacceptable for patients to be subjected to a barium enema evaluation without having had prior proctosigmoidoscopic examination.

The most important reason for avoiding a single-contrast barium enema study in patients in hospital who have hematochezia may be its distinct insensitivity. The Tedesco series (Table 2) classified patients into two categories[1]: 173 patients had no abnormalities on a barium study and 85 patients had only colonic diverticula. Among the 173 who had normal findings on barium enema studies, 91 (or 53%) actually had another lesion picked up by subsequent pancolonoscopy. In those who had only colonic diverticula noted on barium enema evaluation, 42% had another lesion detected by pancolonoscopy. Overall, the false-negative rate for a single-contrast barium enema in patients with hemodynamically significant hematochezia and no abnormalities seen on proctoscopy was 50%! It really makes no sense, therefore, to do this examination in inpatients who have brisk hematochezia.

TABLE 2.—*Barium Enema and Colonoscopic Findings in 258 Patients With Rectal Bleeding**

Barium Enema		*Colonoscopy*	
Findings	*Patients*	*Findings*	*Patients*
Normal	173	Normal	82
		Cancer	20
		Polyps	28
		Inflammatory bowel disease	17
		Telangiectasia	11
		Ischemic disease	2
		Irradiation colitis	1
		Incidental lesions	11†
		Incomplete examination	1
Diverticula only	85	Diverticula only	48‡
		Cancer	9
		Polyps	11‡
		Telangiectasia	6
		Inflammatory bowel disease	2
		Bleeding ileocecal valve	1
		Incidental lesions	7†
		Incomplete examination	1

*From Tedesco et al.[1]
†Incidental lesions are defined as polyps 5 mm or less in size.
‡Colonoscopy was successful on second attempt (one patient).

What about the air-contrast barium enema study for patients with hematochezia? There has been some resistance in the medical community to accepting the air-contrast barium enema study because it requires more time and attention on the part of radiologists. Patients must be better prepared in terms of cleansing the colon of debris because the examination uses a finely dispersed, micropulverized, high-density barium suspension, followed by a rectal insufflation of gas. Thoeni and Menuck studied the sensitivity of single- versus double-contrast barium radiography for polypoid lesions and compared the results with those of colonoscopy.[2] Their data for the sensitivity of single-contrast barium enema studies were similar to those of the Tedesco series. Whereas 45% of the polyps were missed by a single-contrast barium enema study, only 12% of the polyps were undetected by double-contrast barium enema.

Colonoscopy

Colonoscopy is very sensitive in picking up polypoid lesions, more sensitive than either single- or double-contrast radiography. The real problem with colonoscopy has been the difficulty in carrying out the procedure in bleeding patients who have not had rigorous colonic cleansing.[3-7]

The feasibility of colonoscopy as the first diagnostic procedure in patients without prior air-contrast barium enema studies has been studied in 176 patients, 111 of them having had a prior barium enema test.[8,9] Of these patients, 60% underwent air-contrast barium enema evaluation as their first diagnostic procedure, followed by the pancolonoscopy. Once again, using this approach, only 58% of the polyps, two thirds of the cancers and 40% of the cases of colitis were actually detected by double-contrast barium radiography. These patients then had pancolonoscopy, polyps were removed by loop cautery and other lesions were determined. The investigators then prospectively studied 65 other patients who had hematochezia, using colonoscopy as the first procedure. In these patients, the colonoscopists did not have a "road map" to tell them where to look for the polyps or where to look for abnormal mucosa. In these 65 patients, 67 lesions were detected. Following discharge from the hospital, the patients underwent follow-up air-contrast barium enema studies. No additional polypoid lesions and no other mass lesions were noted by follow-up double-contrast radiography. Colonoscopy is thus feasible and accurate without prior barium studies.

There are only two studies in the literature, both in abstract form, that examined the utility, the feasibility and the yield of early colonoscopy as the first diagnostic procedure in patients with brisk hematochezia.[10,11] The studies were by Forde at Columbia-Presbyterian Hospital in New York and Jensen and colleagues at the University of California, Los Angeles. In their combined series of 65 patients, taking the strategy of preparing the patients emergently overnight and doing the colonoscopy in the morning after admission, the number of patients who had no lesions detected dropped from the 30% in the Tedesco series to 15% in the Forde-Jensen

data. In 12% of the patients who were admitted with hypovolemia-associated hematochezia (all of whom had negative nasogastric tube aspirates), 12% were ultimately found to be bleeding from an upper gastrointestinal tract source! When these 65 patients had colonoscopy emergently, the single most common identifiable cause of the hematochezia in these patients was angiodysplasia—25% of total, a considerably higher frequency than the 6.6% in the Tedesco series. Colonic diverticular hemorrhage decreased in frequency from 19% to 14%.

Bowel preparation for colonoscopy. One of the major advances in the approach to patients with hematochezia and a procedure that is now available in almost all hospitals is the use of oral electrolyte solutions to prepare patients.[3-7] We recommend this approach very strongly in preparing patients for emergent colonoscopy. The substance is called GoLYTELY and it is an orally given colonic lavage solution that is available commercially (Table 3). The electrolyte concentration and osmolarity are nearly identical to ileal effluent. The main advantage of this mixture compared with Ringer's lactate solution or saline is that sulfate, the major osmotically active ion in GoLYTELY, is nonabsorbable, therefore retaining the sodium and potassium in the lumen. The major osmotically active substance is polyethylene glycol, a nonmetabolizable substance.[3] Because most patients with hematochezia are older patients, considerable concern was initially raised over administering 4 to 5 liters of an electrolyte solution to elderly patients in preparation for colonoscopy. The safety and the efficacy of this particular mixture have been validated. DiPalma at Wilford Hall Air Force Hospital in San Antonio randomly selected patients to receive clear liquids, magnesium citrate and enemas; a low-residue diet; a normal diet with a rigorous irritant and saline cathartic, or a normal diet up until the midnight before the colonoscopic evaluation and then 5 liters of GoLYTELY given orally with 10 mg of metoclopramide hydrochloride orally (Table 4).[6] In patients given GoLYTELY, the average weight loss was only .45 kg (1 lb), compared with the 1 to 2 kg (3 to 5 lb) that most patients lost with the more rigorous irritant cathartic preparation (Table 5). There were no significant alterations in serum sodium, potassium or bicarbonate values when using 5 liters of oral GoLYTELY solution. Moreover, comparing the irritant cathartic-treated patients with those given GoLYTELY, breath hydrogen and methane levels dropped precipitously in both groups of patients, documenting adequate evacuation of flammable colonic gases.[6] With 5 liters of GoLYTELY, 92% of the patients were adequately prepared for colonoscopy compared with lesser percentages of patients with the standard colonic preparations. There was some abdominal fullness but an enhanced willingness to repeat the GoLYTELY oral preparation when compared with standard evacuation protocol.[5]

TABLE 3.—*GoLYTELY Colonic Lavage (Oral Administration) Braintree Laboratories, Inc, Braintree, Mass*

Composition	*(mmol/liter)*
Sodium chloride	25
Sodium sulfate	40
Potassium chloride	10
Sodium bicarbonate	20
Polyethylene glycol	80 (60 grams/liter)
Electrolyte Concentrations	*(mEq/liter)*
Sodium	125
Potassium	10
Chloride	35
Bicarbonate	20
Sulfate	80
Polyethylene glycol 3,350	599

Final osmolarity—263 mosm/kg of body weight

Standard administration: ½ to 1 liter/h for a total of 4-5 liters

Angiography and Technetium Scintigraphy

Angiography and nuclear scans have valuable roles in evaluating patients who have hematochezia.[12-14] The greatest difficulty encountered with angiography and technetium scintigraphy is the insensitivity in patients with modest hematochezia. The published sensitivity for angiography is 0.5 ml per minute, or detection of as little as 30 ml per hour of blood loss. In our experience, unless patients are bleeding about one unit of blood per hour, an angiogram is unlikely to be abnormal. Because about 10% to 15% of the bleeding lesions in patients with vigorous hematochezia are from the upper gastrointestinal tract, celiac artery angiography must be done in bleeding patients with normal inferior and superior mesenteric angiograms. Tolazoline hydrochloride, a vasodilator,

TABLE 4.—*Colon Cleansing Methods**

Time	*Group†*			
	1 (64)	*2 (40)*	*3 (44)*	*4 (49)*
Days 1 and 2	Clear liquids	Minimum-residue diet	Normal diet	Normal diet
Day 3	Clear liquids	Minimum-residue diet	Minimum-residue diet	
1200 hours	Magnesium citrate‡	Magnesium citrate‡	Magnesium citrate‡	
1600 hours	X-Prep§		Bisacodyl tablets‖	
Bedtime	Enema¶	Enema¶	Enema¶ and bisacodyl suppositories#	
2400 hours	NPO	NPO	NPO	NPO
Day 4	Enema¶	Enema¶	Enema¶	Metoclopramide,** GoLYTELY

NPO=nothing by mouth

*From DiPalma et al.[6]
†Numbers in parentheses are the number of patients in each group.
‡240 μl of chilled magnesium citrate.
§X-Prep Bowel Evacuant Kit; 240 μl of standardized extract of senna fruit (Gray Pharmaceutical Co, Norwalk, Conn).
‖Four 5-mg bisacodyl tablets.
¶Tap-water enema using 1 liter of water.
#Two 10-mg bisacodyl suppositories.
**Metoclopramide hydrochloride, 10 mg orally.

may be administered intraarterially to better define bleeding lesions. Angiography rarely diagnoses the cause of the hematochezia, but does locate the site of hemorrhage.[12]

Technetium scintigraphy, now available in most hospitals, is done by labeling a patient's own erythrocytes in vitro or in vivo with technetium Tc 99m pertechnetate. The procedure that we use at San Francisco General Hospital is to give an injection first with pyrophosphate and then with technetium pertechnetate, which binds to the pyrophosphate. The patient's own erythrocytes are therefore labeled and the abdomen may be scanned for as long as 20 hours (Figure 1). The published sensitivity is 0.05 ml per minute, or about ten times that of angiography. In general, if patients are bleeding one unit every two to four hours, technetium scintigraphy is likely to be abnormal. Scanning must be done frequently to avoid misinterpretations.[14] In some instances, proximal lesions will bleed intermittently and, with rapid intestinal transit, the radionuclide will localize in the distal bowel, giving the erroneous impression that the bleeding site was distal. A similar problem occurs with distal colonic bleeding sources in which blood backwash can occur, giving the erroneous impression on scan that the bleeding site is from the more proximal colon. In many centers, the technetium scintiscans are required studies before doing angiography. With nuclear scintigraphy, information is available regarding the site of hemorrhage, but again not the cause.

Suggested Approach to Patients Who Have Hematochezia

Taking these new procedures into consideration, what recommendations can be made in evaluating patients with hematochezia? (Figure 2). First of all, one must clearly document

TABLE 5.—*Comparison of Weight, Hematologic Changes and Biochemical Changes**†

Measurement	*Group*‡ 1	2	3	4
Weight, lb	−4.1±2.7 (53)	−4.5±3.6 (37)	−3.0±2.1 (42)§	−1.3±2.1 (47)‖
Hemoglobin, grams/dl	0.4±0.1 (55)	0.7±0.1 (33)	0.4±0.6 (38)	0.2±0.7 (48)
Hematocrit, %	0.6±0.3 (55)	1.7±2.9 (33)	1.0±0.8 (37)	0.7±1.8 (48)
Specific gravity	−0.005±0.008 (54)	−0.002±0.001 (33)	−0.002±0.006 (38)	0.004±0.009 (45)‖
Urine osmolarity, mosm	ND	ND	−49.8±214 (41)	34.6±248 (41)
Sodium, mEq/liter	−1.1±6.0 (57)	−1.7±3.5 (36)	0.7±3.8 (40)	0.7±4.2 (46)
Potassium, mEq/liter	−0.19±0.5 (56)	−0.3±0.5 (37)	0.06±0.56 (40)§	−0.2±0.5 (46)
Chloride, mEq/liter	−0.2±0.4 (56)	−0.69±6.3 (36)	−0.7±3.4 (40)	−1.8±3.4 (46)
Carbon dioxide, mEq/liter	−0.8±0.5 (55)	−0.7±0.5 (34)	0.0±1.1 (4)	2.2±2.9 (8)
Blood urea nitrogen, mg/dl	−4.7±5.2 (52)	−3.4±0.5 (35)	−3.1±3.7 (40)	−0.6±3.0 (46)‖
Creatinine, mg/dl	0.09±0.3 (55)	0.04±0.3 (36)	0.01±0.15 (40)	−0.03±0.2 (46)
Calcium, mg/dl	ND	ND	0.14±0.5 (27)	−0.8±0.4 (33)
Phosphate, mg/dl	ND	ND	−0.05±0.7 (27)	−0.16±0.5 (33)
Albumin, grams/dl	ND	ND	0.04±0.2 (27)	0.1±0.2 (33)
Magnesium, mEq/liter	ND	ND	0.1±0.2 (27)‖	0.0±0.01 (32)

NO=not done

*From DiPalma et al.[6]
†Values given as mean ± standard deviation. Numbers in parentheses are the number of samples analyzed.
‡See Table 4 for the number of patients in each group
§$P < .05$.
‖$P < .001$.

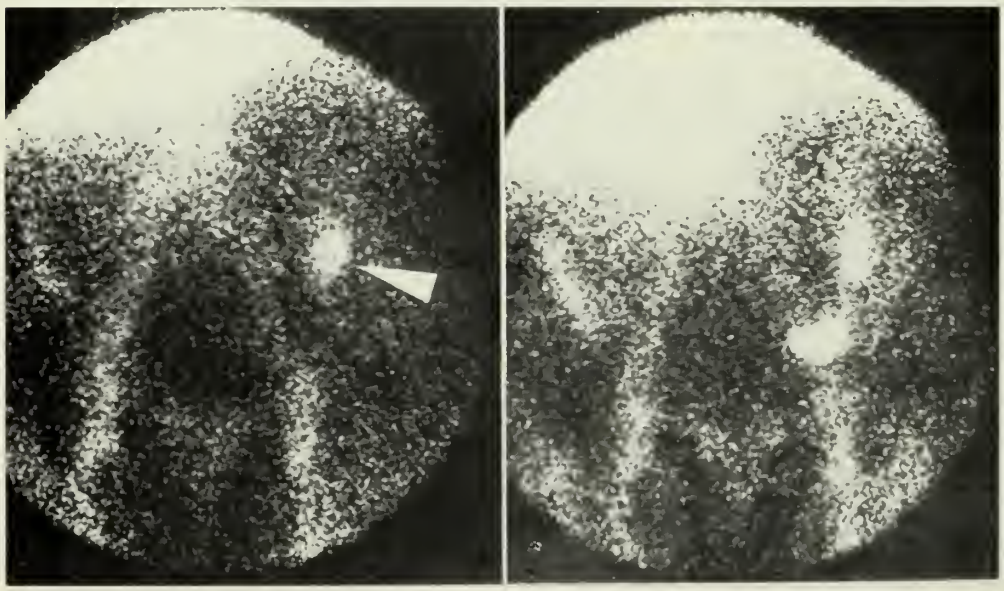

Figure 1.—Technetium scintiscans in a patient with hemorrhage from the sigmoid colon **(arrow)**. The iliac and femoral arteries are also clearly outlined. (Reprinted with permission from Martisz et al.[14])

that there is hematochezia and that bleeding is not from the vagina or from the urethra. Anoscopy and digital and sigmoidoscopic examinations are essential in every bleeding patient at the time of the first visit. Because about 10% to 15% of patients with hemodynamically significant hematochezia are actually bleeding from the upper gastrointestinal tract, one must look very carefully for this possibility.

A nasogastric tube lavage is mandatory in all patients with vigorous hematochezia. If there is any evidence of fresh blood or "coffee-grounds" blood on lavage, endoscopy must be done following sigmoidoscopy. If following vigorous lavage there is no blood but also no bile obtained, the lavage is not adequately sampling the contents of the duodenum. A posterior duodenal bulbar ulcer cannot be excluded by this negative lavage. If the patient is hypotensive, is briskly bleeding, has active bowel sounds or has a history of dyspepsia or confirmed peptic ulcer disease, endoscopy should be part of the initial evaluation of patients with hematochezia who have positive or equivocal results on gastric aspirate. If the results of sigmoidoscopy are truly normal, the physician must reevaluate the patient for the next diagnostic procedure, based on the estimated briskness of the hemorrhage. If hemorrhage is judged to be more than one unit every one or two hours, then an angiogram is likely to be abnormal and it should be the next diagnostic procedure. If bleeding is intermittent with a transfusion requirement of only one unit every two to four hours, a technetium scintiscan can and should be done with frequent scanning intervals. If, however, there is no active bleeding after initial stabilization, the patient should be given GoLYTELY lavage solution and colonoscopic evaluation done within a reasonable period of time. Overnight lavage preparation is acceptable, and the examination can be done within a day of admission for those patients who cease bleeding once they have been admitted to hospital.

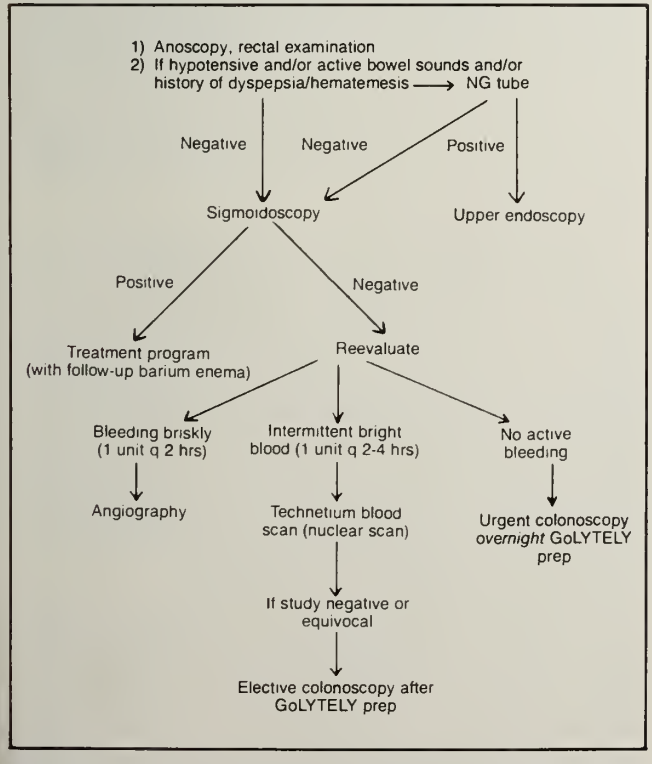

Figure 2.—Suggested approach to patients admitted to hospital with hematochezia. Nasogastric (NG) tube lavage and sigmoidoscopy must precede additional tests.

Diverticular Hemorrhage

I would like now to turn to two specific causes of hematochezia, the two most common identifiable causes of hematochezia when proctoscopy shows no abnormalities. The first is colonic diverticular hemorrhage. Diverticulosis is pervasive in western societies and 50% of persons older than 50 years will be found on routine barium enema evaluation to have colonic diverticula. Diverticula are associated with low-residue diets in animal species that have teniae coli—that is, longitudinal smooth muscle of the colon grouped into bands of musculature. Colonic diverticula in humans always develop on the mesenteric side of the two antimesenteric teniae.[15] The outpouchings of colonic mucosa develop through obliquely arranged tissue septa in circular smooth muscle. As a diverticulum protrudes, it carries with it on its dome a subtended, perforating, mesenteric arteriole that perfuses the mucosa and the submucosa of the adjacent bowel (Figure 3).

The pathophysiologic sequence for the development of diverticular hemorrhage is poorly understood.[15] Pathologically, it appears that there are eccentric intimal changes and finally eccentric vessel rupture (Figure 4). Clinically, colonic diverticular hemorrhage never occurs together with diverticulitis. Thus, most patients with diverticular hemorrhage usually have no symptoms of diverticulitis and may have little history of colonic dysfunction. Often the first manifestation of diverticular disease in many patients is brisk hemorrhage. Moreover, although 85% to 90% of colonic diverticula are

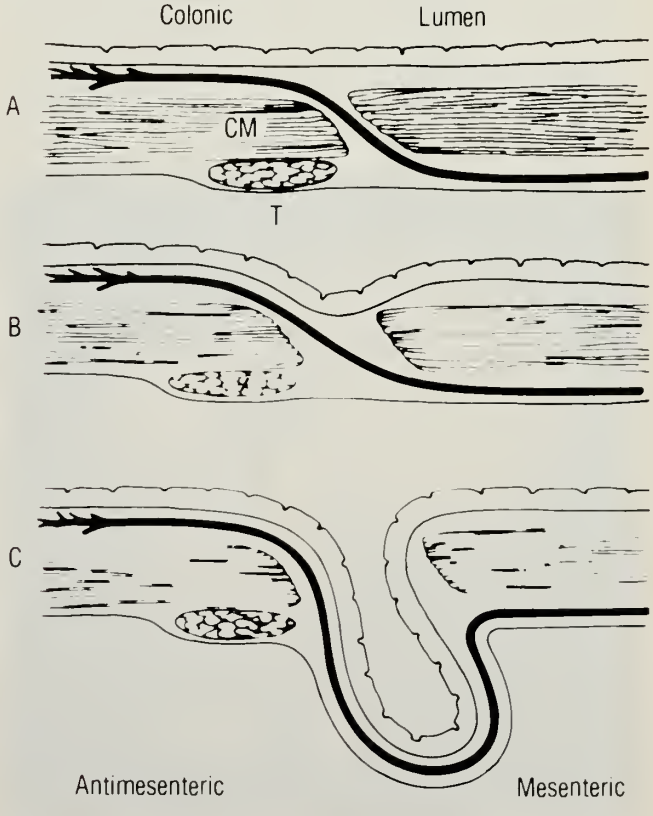

Figure 3.—Development of a colonic diverticulum. The outpouching of colonic mucosa (**CM**) through a tissue (**T**) septum carries with it a mesenteric arteriole. (Reprinted with permission from Meyers et al.[15])

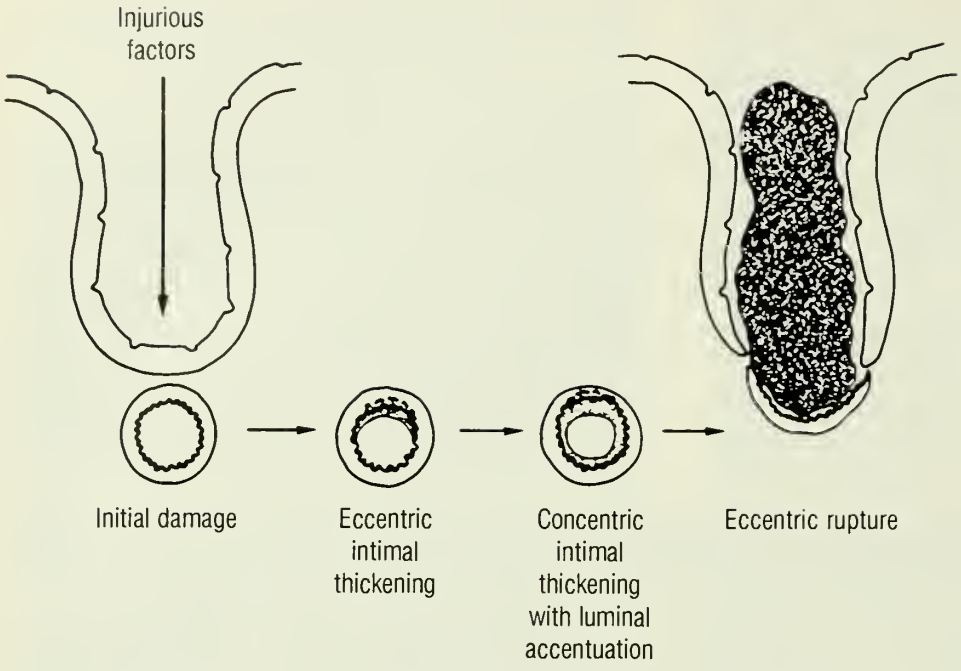

Figure 4.—Suggested sequence of diverticular hemorrhage. Hemorrhage rarely develops during the course of clinical diverticulitis. (Reprinted with permission from Meyers et al.[15])

located in the descending or sigmoid colon (where diverticulitis commonly occurs), more than 50% of cases of colonic diverticular hemorrhage are from the ascending colon or the cecum.[16]

Angiography will accurately pinpoint a site of brisk diverticular hemorrhage, but may not determine the cause of the colonic bleed. There have been considerable advances in the management of patients with diverticular hemorrhage using angiographic techniques.[13,17-19] With angiographic administration, it is possible to control the hemorrhage in the vast majority of patients with either administration of vasopressin alone or by occluding the bleeding vessel with embolic material. In primates, there is a profound decrease in mesenteric artery flow rates with angiographically administered vasopressin. The optimal dose in primates appears to be 0.005 units per kg of body weight per minute or about 0.35 units per minute of continuous, intraarterial infusion in a 70-kg (154-lb) person.[17] Unfortunately, at this dose range when vasopressin is given intraarterially, there is still substantial systemic toxicity. Arterially administered vasopressin at this dose will produce nearly a 25% decrease in cardiac output and sizable increases in peripheral vascular resistance and blood pressure. Nonetheless, angiographic vasopressin infusion does control colonic hemorrhage.[18,19] In addition, embolization using autogenous clot or other agents can arrest hemorrhage from colonic diverticula.[18,19] There are unfortunately no controlled trials of angiographic embolization procedures in which patients were randomly selected for either an operation or embolization. Further studies are desperately needed.

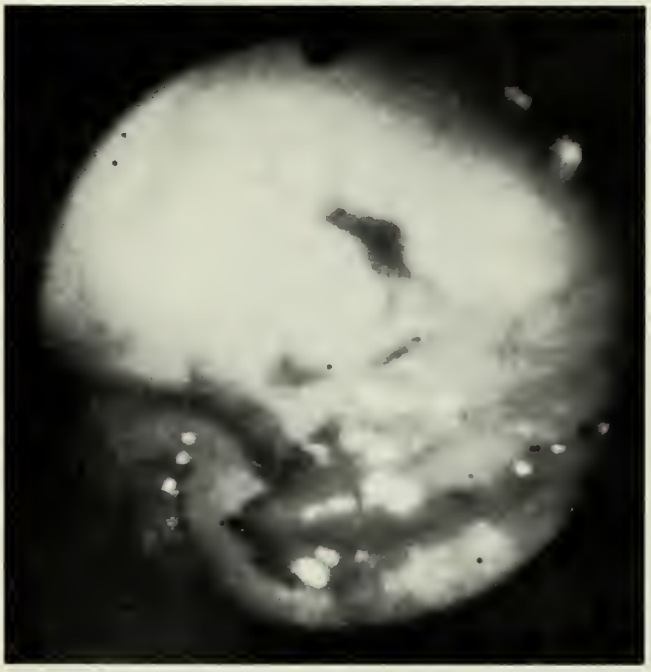

Figure 5.—Colonoscopic picture of cecal angiodysplasia. A central arteriole gives off radiating smaller vessels.

Colonic Angiodysplasia

Angiodysplastic lesions of the colon have been noted with increasing frequency, particularly in elderly patients, many of whom have severe underlying cardiopulmonary disease.[20-24] Many of these lesions are small spiderlike telangiectasias (Figure 5). Some of them actually assume an angiomatous appearance with large, almost polypoid, prominences. Histopathologically, angiodysplasia consists of dilated submucosal arteries, capillaries and veins. These lesions look similar to the spider angiomata that are noted on the chests of patients with cirrhosis.[20] Unfortunately, these colonic lesions are extremely thin-walled and precariously located just beneath the overlying columnar epithelium of the bowel.

In addition to the angiographic embolization techniques that have been popular now for the past ten years, these lesions have been successfully treated by a variety of coagulation procedures. Colonoscopic argon laser coagulation has been used in three to four different centers, including ours at San Francisco General Hospital.[23,24] The blue-green light of the argon laser is preferentially absorbed by the bright red of the angiodysplastic lesions. Coagulation depth with the argon

laser is only 2 mm, enhancing its safety in the thin-walled colon. The colonoscope is first passed to locate the abnormal area. Through the biopsy channel of the colonoscope, a polyethylene catheter containing a 400-micron quartz fiber is passed to transmit the blue-green laser light. A two-stage foot switch allows the operator to first aim at the target, then apply full treatment power. A white coagulum is produced. The most important change that occurs is not, however, the initial coagulation of the vessel but rather the subsequent development of an intense fibrotic reaction around the coagulated vessel. A localized barrier of dense fibrous tissue is thus developed between the overlying epithelium and the underlying vascular network. There are two studies in the literature, both in abstract form: Bowers and Dickson at Salt Lake City studied patients with angiodysplasia in the bowel treated with the argon laser. There was a decrease in both bleeding episodes and transfusion requirements in their series.[23] Jensen and associates likewise found a significant rise in the mean hematocrit over a 14-month period following argon laser endoscopy treatment.[24] In our own experience with nearly 40 patients with colonic angiodysplasia treated with the argon laser, nearly 80% have had no further bleeding.

In summary, there have been very dramatic and substantial advances in our approach to patients with hematochezia. Several exciting new treatment modalities have been recently developed. The evaluation of the patient with hematochezia requires a conscientious approach based on the estimated briskness of the hemorrhage.

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Epitomes

Important Advances in Clinical Medicine

Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Intraarterial Chemotherapy

COLORECTAL CANCER affects 138,000 new patients and is responsible for approximately 60,000 deaths each year in the United States alone. Most patients who die of colorectal carcinoma have liver metastases, and for many the liver is the only clinical site of metastatic tumor. Chemotherapy for patients with metastatic disease consists of the fluorinated pyrimidines 5-fluorouracil (5-FU) and fluorodeoxyuridine (FUDR, or floxuridine). While 5-FU and floxuridine produce objective response rates of about 20% when given intravenously, neither has been proved to provide a survival advantage over no treatment.

A number of factors predict that 5-FU or floxuridine given via the hepatic artery may be superior to intravenous delivery in patients with liver-only metastasis from colorectal carcinoma. The blood supply of hepatic metastasis is primarily via the hepatic artery, whereas a normal liver receives a dual blood supply from the hepatic artery and portal vein. Thus, administering 5-FU or floxuridine into the hepatic artery exposes hepatic metastasis to a higher concentration of drug than normal liver tissue. Pharmacologic properties of 5-FU and floxuridine that may make hepatic artery therapy more effective include a favorable dose-response curve and high rates of first-pass hepatic extraction (80% and 95%, respectively), thus minimizing systemic toxicity. The cell-cycle phase-specific activity of 5-FU and floxuridine predicts increased cytotoxicity with long-term drug use such as is achievable with continuous infusion. The recent development of a reliable, implantable, continuous infusion pump has made hepatic artery infusion chemotherapy practicable. For these reasons, hepatic artery infusions, usually with floxuridine, have become an active area of clinical investigation.

The reported series of colorectal cancer patients treated with hepatic artery infusion have either been uncontrolled or historically controlled and are difficult to assess because they use a broad range of methods and criteria to measure response. Computed tomography, especially when done with volumetrics, is the single most objective and reliable index of disease response or progression. Radionuclide liver scans are reproducible but difficult to quantify in determining response. Although physical examination, liver enzymes and carcinoembryonic antigen levels are all unreliable methods of measuring the response of colorectal cancer metastatic to the liver, they have been used in many studies as indicators of disease response. Despite these frequently inexact methods of assessing response, the available studies of hepatic artery infusion of floxuridine have found impressive response rates ranging from 29% to 88%. In addition, some of these studies report superior durations of survival when compared with historical control groups. Whether these improved rates of response and survival are the result of variations in the tumor burden at the initiation of therapy, the methods of assessing response, the use of inappropriate control groups or of the efficacy of treatment is uncertain.

Hepatic artery infusion of floxuridine is associated with significant toxic effects, especially biliary sclerosis, which occurs in most patients. Recent evidence suggests that the "chemical hepatitis" reported previously may in fact have been biliary sclerosis. This is a serious toxic effect and has been documented by cholangiography, liver biopsy and at postmortem examination. It is heralded by elevation of the alkaline phosphatase level, and a doubling of the alkaline phosphatase level requires at least delaying further administration of the drug until the levels return to normal, with attenuation of further doses. The anatomic changes of biliary sclerosis are presumably not reversible and may contribute to drug-related mortality, although the associated elevations in alkaline phosphatase and bilirubin levels may resolve with the early withdrawal of therapy.

Gastric and duodenal inflammation and ulceration and cholecystitis are other complications of hepatic artery infusion of floxuridine. These complications appear to be related to the incidental perfusion of the involved organs by floxuridine. The frequency of the gastric and duodenal complications can be minimized at the time of pump implantation by ligating the gastroduodenal artery and collaterals that arise distal to the point of cannulation of the hepatic artery. Most investigators recommend routine cholecystectomy at the time of placement of the infusion pump to prevent the development of drug-induced cholecystitis.

No prospectively randomized studies comparing the efficacy and toxicity of intravenous with intraarterial administration of 5-FU or floxuridine have yet been completed. Appropriately designed, prospectively stratified, randomized trials comparing intravenous administration with hepatic artery infusion of chemotherapy for colorectal carcinoma metastatic to the liver only are in progress in the Northern California Oncology Group (headquarters in Palo Alto) and at the Memorial Sloan-Kettering Cancer Center (New York). Definitive conclusions regarding the precise role of hepatic arterial infusion chemotherapy must await the completion of these studies.

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The Routine Preoperative Chest X-ray Study

ACCORDING TO THE REPORT of a World Health Organization (WHO) Scientific Group, "There are some excellent studies on the futility of preoperative chest radiography," a conclusion that was reached after a comprehensive study of the relevant international medical literature. This opinion is endorsed by the Food and Drug Administration, the US Bureau of Radiological Health and most of the American specialist colleges and societies. If the results of a clinical examination are normal, no preoperative chest x-ray film is needed at any age for any surgical procedure. Moreover, even when there are clinical chest symptoms, there is little advantage to be gained in most cases because clinical judgment will decide the choice of anesthesia with as much accuracy as a chest x-ray study. Nor will postoperative management be affected by information gained from a preoperative chest film, which is not only not cost-effective but increases the radiation given both to an individual patient and to the population. Indeed, it is time that the routine chest film cease to be part of a routine physical examination, preoperatively or otherwise; the only exception may be in populations wherein chest disease is known to be prevalent.

The WHO Scientific Group on the Indications for and Limitations of Major X-Ray Diagnostic Investigations concluded that

> provided a careful clinical examination is made and there is no clinical evidence of chest disease, there is no indication for preoperative chest radiology. If the clinical examination discloses an abnormality, this in itself is not necessarily an indication for radiography. Such cases must be judged on their merits.

The available references are numerous; only a selection can be provided here.

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Fine-Needle Aspiration Biopsy of Thyroid

THYROID NODULES are common and about 4% or 40,000 per million persons in the United States have nodular goiters. Thyroid cancer, however, is rare: about 40 cases per million persons. Thus, great selectivity is necessary in deciding which nodules are likely to be malignant and to require aggressive surgical management.

Fine-needle aspiration biopsy of the thyroid has largely solved this dilemma. Introduced by Soderstrom in 1952, it has been used widely in Sweden, Europe and Japan. Only in the past ten years, however, with the development of a cadre of trained cytologists, has fine-needle aspiration biopsy been widely used in the United States.

Fine-needle aspiration biopsy of the thyroid is a simple office procedure, nontraumatic, acceptable to patients and easily repeated if necessary. If the aspirate is diluted with blood, or not enough thyroid tissue is obtained, it must be repeated. Other than an occasional tiny hematoma at the site of aspiration, there have been no complications. There has been no spread of cancer with this technique.

A physician will usually receive one of three reports from the cytologist: (1) clearly malignant, (2) clearly benign or (3) follicular neoplasm or suspicious for neoplasm.

Papillary, medullary, anaplastic and metastatic neoplasms are easily diagnosed and, if present, require surgical confirmation and appropriate therapy. Clearly benign lesions include involutionary nodules, benign thyroid nodules, chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), subacute thyroiditis and multinodular goiter. Patients with these lesions are usually treated with levothyroxine to suppress thyroid-stimulating hormone and growth. Follicular neoplasms are usually benign (about 85%) but occasionally malignant (15%). If the lesion is large (more than 2 cm), firm or has shown recent growth, it should be surgically removed. If it is small and soft, the patient can be given a trial of thyroxine therapy for three to six months. If the lesion fails to regress or grows, then it should be removed. Cysts of the thyroid can

easily be evacuated by this technique and they are rarely malignant (less than 5%). Malignant lesions will usually recur, with bloody fluid and evidence of internal echos on ultrasound scan. If thyroid cysts do recur after two or three aspirations, they probably should be surgically removed.

False-positive results—that is, a diagnosis of cancer in a benign lesion—occur in about 4% of aspirations, and false-negatives—that is, a diagnosis of a benign lesion in the presence of malignancy—in about the same percentage. Thus, the method is both sensitive and specific. Note that fine-needle aspiration biopsy can be used in the diagnosis of other neck masses, such as metastatic cancer or Hodgkin's disease.

Fine-needle aspiration biopsy of the thyroid is probably the most important advance in the management of thyroid nodules in the past decade. It has enabled physicians to avoid delay in the diagnosis of thyroid malignancy and to avoid an unnecessary operation for benign thyroid lesions. As the initial screening test, it will reduce by half the cost of evaluating a thyroid nodule.

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New Criteria for the Diagnosis of Alzheimer's Disease

WITH THE INCREASED publicity concerning Alzheimer's disease, the development of state initiatives for diagnosing and treating cases of Alzheimer's and the appearance on the horizon of a number of experimental therapies, the accurate diagnosis of this disorder becomes important. Unfortunately, there is no biochemical or radiographic marker upon which a clinician can rely. In 1980, the American Psychiatric Association in the third edition of its *Diagnostic and Statistical Manual* (DSM-III) proposed criteria that have been widely accepted for the clinical diagnosis of Alzheimer's disease. However, these criteria have been found to apply to only about half of the Alzheimer patients because the disease presents in a greater variety of ways than first believed. Thus, under DSM-III criteria, a patient with Alzheimer's disease was required to have impairment not only of memory, but of at least one other area of cognition; the course was described as having an insidious onset with a steady progression, and, most important, other neurologic or systemic disorders that can produce dementia had to be excluded.

In reality, it has been found that in some patients Alzheimer's disease may begin primarily as a memory, language or constructional deficit that may progress for several years before becoming more generalized. The course is always one of deterioration, but in some patients it may be interrupted by plateaus lasting for several years.

Particularly in older patients with Alzheimer's disease, the coincidence of an Alzheimer process with a single stroke, with thyroid disturbance, vitamin B_{12} deficiency and so forth, may occur. To account for these deviations and to provide a wider umbrella for physicians, a work group under the auspices of the Department of Health and Human Services Task Force in Alzheimer's Disease arrived at the following recommendations:

1. A diagnosis of *definite* Alzheimer's disease requires clinical criteria for probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.
2. The criteria for a clinical diagnosis of *probable* Alzheimer's disease are similar to those of the original DSM-III and include the following:
   - There must be a dementia established by clinical examination and documented by a mental state test that includes deficits in two or more areas of cognition;
   - There should be progressive worsening of memory and other cognitive functions;
   - No disturbances of consciousness;
   - The absence of systemic disorders or other brain diseases that, among themselves, could account for progressive deficits.

This diagnosis of probable Alzheimer's disease is similar to that originally described in DSM-III.

Critical to the diagnosis of dementia is the documentation of the cognitive deficit by the use of mental state tests such as the Mini-Mental Test or a similar examination. The importance of tests of mental state is emphasized because patients with dementia early in the course of their disorder may maintain good social conversation and may not be obviously demented during routine history taking. Laboratory features consistent with a diagnosis of probable Alzheimer's disease include a computed tomographic scan normal for age or with evidence of cerebral atrophy, a normal electroencephalogram or one with increased slow-wave activity and normal findings on a lumbar puncture. Often there is a family history of similar disorders. As the disease progresses, there is impairment of activities of daily living and altered patterns of behavior. There may be associated symptoms of depression and decreased cognizance, delusions, hallucination, verbal or physical outbursts, sexual disorders and weight loss. Usually there are no focal neurologic findings such as hemiparesis, sensory loss, visual field deficits or incoordination early in the course of Alzheimer's disease.

A third category of diagnosis is that of *possible* Alzheimer's disease. This category includes patients who have a progressive dementia but have either a variation in the onset, presentation or clinical course or a systemic or brain disorder that is enough to produce dementia, but it is not considered to be the cause of dementia because, when treated, the dementia continues to progress. Among the variations of onset is a subgroup of patients who present with a progressive deterioration in a single area of cognitive function, such as aphasia, apraxia or agnosia, or a pure memory deficit for several years before the development of a more generalized disorder. Such patients, however, must be investigated for the possibility of focal neurologic disease.

These criteria emphasize both the normal history and progression seen in patients with Alzheimer's disease and the continued need to exclude other disorders that may produce a

dementia syndrome. Among the more common disorders that must be excluded are multi-infarct dementia, bipolar depressive disorders and drug intoxications. Other disorders that may occur and produce dementia include thyroid disease, pernicious anemia, neurosyphilis, Creutzfeldt-Jakob disease, subdural hematoma, normal pressure hydrocephalus, Huntington's disease and a brain tumor. The workup of a patient with Alzheimer's disease requires an accurate medical history, neurologic, psychiatric and clinical examinations and laboratory studies to exclude these other diagnoses. Widespread adoption of these recommended criteria for the clinical diagnosis of Alzheimer's disease would lead to improved communication among the physicians caring for patients with this devastating disorder.

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Clinical Use of Platelet-Suppressant Drugs

ASPIRIN, by inhibiting cyclooxygenase, blocks the formation by the platelet of thromboxane A_2, the most powerful natural potentiator of platelet aggregation. The effect is prolonged, probably for the life span of the platelet, and can be shown in vivo by a prolonged bleeding time. As cyclooxygenase is required also by endothelial cells to form prostacyclin, which inhibits platelet aggregation, there has been some concern that the overall effect of aspirin might not be to reduce arterial thromboembolism. There have been many clinical trials with aspirin and other drugs that interfere with platelet function and analysis of these as a group allows us to make some clinical recommendations.

Aspirin can reduce (by about 5% in the first year) the risk of sudden death and of myocardial infarction in persons with a high risk of these incidents, namely, those who have had a recent transient ischemic attack or myocardial infarction or who have unstable angina. In two studies the frequency of coronary artery bypass graft occlusion was reduced by aspirin therapy initiated shortly before or immediately after an operation. There is also evidence that aspirin reduces the risk of stroke and sudden death following a transient ischemic attack and that it is effective in preventing thromboembolic complications in patients with essential thrombocythemia and polycythemia and the occlusion of arteriovenous shunts. The studies as a whole show a significant reduction in morbidity for men only because the number of women studied was too small, but there is no known pharmacologic or physiologic reason why the effect should be sex-dependent. The benefit is greater the earlier the aspirin therapy is started and is apparent within the dose range of 100 to 1,000 mg a day. Aspirin is contraindicated in those with other acquired or inherited hemostatic deficiencies, in patients with significant dyspepsia or with previous gastrointestinal bleeding; these considerations will exclude about 10% of otherwise suitable patients.

Although a beneficial trend has been noted in the trials of sulfinpyrazone in patients with transient ischemic attacks, the results are not statistically significant, and neither this drug nor dipyridamole can yet be recommended for routine use either alone or combined with aspirin. There is no indication for using aspirin to prevent embolization from prosthetic heart valves, for which anticoagulants remain the first line of therapy, with sulfinpyrazone giving added benefit.

Many questions remain to be answered, including the most effective dose of aspirin, the duration of treatment, the role of combination therapy with other platelet-function-altering drugs and the evaluation of new drugs, particularly ticlopidine hydrochloride, pentoxifylline and ketanserin. Clinical trials designed to study these matters are in progress and their results are eagerly awaited.

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Adjuvant Chemotherapy for Breast Cancer

STAGE I (T_1,N_0,M_0) and stage II (T_1,N_1,M_0, T_2N_{0-1},M_0) breast cancers are potentially curable with local-regional therapy. The risk of recurrence, usually at distant sites, after such therapy is also known. The cause of recurrent disease is microscopic metastatic tumor already present but not identifiable at the time of the initial operation. Given these conditions, administering systemic antitumor therapy as an additional (adjuvant) treatment to eradicate residual tumor, after definitive local-regional therapy, is a rational approach.

Over the past 15 years, dozens of adjuvant therapy trials in breast cancer have been devised and patient accession completed, and the data examined and reexamined for statistical significance and clinical implications. The adjuvant treatments have ranged from two- to five-day courses of a single chemotherapy agent given immediately after surgical treatment, to multidrug chemohormonal therapy combinations given for two years. The early trials concentrated on women with involved axillary nodes (N_1) who were at high risk for recurrence. More recently, node-negative trials have also been initiated. Data analysis has been exhaustive. Updates have been frequently presented and regularly published. Prognostic subgroups have been studied—premenopausal and postmenopausal women, patients with one to three positive nodes versus those with four or more nodes involved, or four to ten nodes versus more than ten nodes. Explanations for the various results seen in different subgroups abound.

Two important benefits may accrue from adjuvant chemotherapy: Improved overall survival is the primary possible benefit of adjuvant treatment and is the one ultimately sought.

However, prolonged relapse-free survival may also be worthwhile. Enhanced relapse-free survival and even improved overall survival must be weighed against possible toxicity, monetary costs and effect on life-style in finally deciding the value of adjuvant therapy as standard care. Therefore, until long-term data are available and a beneficial impact is clear, adjuvant programs should remain within the realm of experimental therapy.

In premenopausal women with metastasis to nodes, numerous studies show significantly prolonged relapse-free survival and some show an overall survival benefit after adjuvant chemotherapy. While single-drug trials show such benefits in some premenopausal subsets, the multidrug adjuvant programs of Bonadonna and co-workers with CMF (cyclophosphamide, methotrexate and 5-fluorouracil), now reported with a ten-year median follow-up, appear broadly efficacious among premenopausal patients. The optimal duration of treatment is under study. In one controlled trial, 6 months of CMF therapy were as good as 12 months. Even shorter programs of more intense therapy may eventually be found to be equally or more useful. Therefore, while giving multidrug adjuvant chemotherapy to node-positive, premenopausal women has achieved the status of "conventional" or "standard" treatment, research trials to further define optimal drugs and treatment schedules are in order. These new trials will not include a "no-treatment" control group.

Data on the efficacy of adjuvant therapy using drugs, hormones or a combination of both for postmenopausal women with involved axillary nodes (N_1) are widely available. A few studies have shown clear benefit, with enhanced relapse-free and overall survival. Others show enhanced relapse-free survival without concomitant overall survival advantage. Still others—slightly more than half of all reported—show no benefit on either count. Some investigators have emphasized the need to give full-dose adjuvant chemotherapy to postmenopausal women to obtain beneficial results. Others, concerned with the toxicity of adjuvant chemotherapy in older patients, have turned to trials of adjuvant hormonal therapies.

The available data stimulate controversy about the place of adjuvant therapy in the management of postmenopausal women with positive nodes. It seems inappropriate to present adjuvant multiagent chemotherapy as "standard" for postmenopausal women based on the evidence of clinical trials thus far. However, enough positive data are available to demand further evaluation of various adjuvant approaches using the mechanism of well-designed, large-scale, cooperative clinical trials. Questions of dose, duration, amount, nature and timing of treatment all warrant investigation. Clinical trials evaluating such issues in node-positive postmenopausal women should ideally include a no-treatment control group, though this issue of study design is highly controversial in and of itself.

Adjuvant therapy for breast cancer has had an important, beneficial impact, especially in premenopausal women with metastasis to nodes. Clearly, however, we are far from having all the answers. Continued commitment among physicians to participate in well-designed trials that both ask important questions and offer the most advanced patient care is crucial. With the strong support of the medical community to continue careful adjuvant therapy trials in breast cancer, the uncertainties extant in the field today should give way to further positive directions over the next several years.

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Cyclosporine—A Powerful New Immunosuppressant

CYCLOSPORINE IS A powerful immunosuppressive drug that has had a major impact on the success of organ transplantation since its introduction a few years ago. It has a unique cyclic endecapeptide structure, which inhibits T-cell activation, without directly affecting B cells, macrophages or any other branch of the immune responses. Unlike its predecessor, azathioprine, cyclosporine has not thus far proved toxic to rapidly proliferating cells such as bone marrow. A further advantage of cyclosporine therapy is the reduced or eliminated requirement for prolonged administration of high-dose corticosteroids, with a resultant improvement in the quality of life for transplant recipients. An unexpected benefit has been a shorter hospital stay and a reduction in the cost of transplantation by as much as 30%.

Cyclosporine use has improved the one-year survival rate of cadaveric renal allografts from 50% to as high as 85%. Similarly, the one-year survival rate of heart transplant recipients has increased from about 60% to 80%. The one-year survival rate of liver transplant recipients has almost doubled, to 70% for children and 50% for adults. Clinical heart and lung transplantation, which was never done successfully before cyclosporine, has now been carried out in more than 20 patients, with a number of long-term survivors. A survival advantage in pancreas and bone marrow transplant patients treated with cyclosporine has not been clearly shown, though it does lower the incidence and severity of graft-versus-host disease. Because of its powerful immunosuppressive properties, the use of cyclosporine is being considered in a number of diseases with purported immune mechanisms. A successful trial of cyclosporine in abolishing insulin requirements among patients with type I diabetes mellitus was recently reported.

Cyclosporine has a number of clinically mild side effects including hirsutism, gingival hyperplasia, nausea and elevated liver enzyme values. In rare cases, there is also central nervous system toxicity including ataxia, quadriparesis, changes in mental state and aseptic meningitis. The incidence of opportunistic infections is similar to that of azathioprine-treated patients, although their severity appears to be reduced. Lymphoproliferative malignant disorders initially ap-

peared to be increased among cyclosporine users but recent experience is reassuring. These B-cell tumors appear to follow reactivation of or infection with Epstein-Barr virus (EBV) and contain the Epstein-Barr nuclear antigen (EBNA) or portions of the EBV genome. These tumors may represent uncontrolled proliferation of virally transformed lymphocytes and respond temporarily to the antiviral agent acyclovir. Reducing or eliminating immunosuppression has also been followed by remission of tumor, albeit associated with graft rejection.

The most serious common side effect of cyclosporine is its nephrotoxicity. In as many as 80% of recipients a significant rise in the serum creatinine level occurs. This appears to involve both glomerular and tubular damage, and it is at least partly dose-dependent. Though renal insufficiency can often be minimized by reducing the dose or by switching the therapy to azathioprine, many patients will have irreversible renal damage and a few require dialysis. Cyclosporine nephrotoxicity is a problem in renal transplantation because it cannot be easily distinguished from graft rejection; it is especially worrisome in heart and liver transplant recipients, in whom reduction of immunosuppression and subsequent graft rejection may result in death. The renal lesion is accompanied by hypertension, which is often very difficult to control.

Cyclosporine has had a favorable impact on the field of organ transplantation, but its long-term utility may be limited or negated by its nephrotoxicity. Clinical studies are currently being done to define the precise role of cyclosporine in organ transplantation. Obviously, caution must be exerted in using this substance in any condition, including diabetes, where morbidity and mortality may be determined by renal function.

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Non-A, Non-B Hepatitis

THE ABILITY TO diagnose hepatitis A, hepatitis B, δ-agent, cytomegalovirus and Epstein-Barr virus infections through specific serologic tests has uncovered a series of patients in whom syndromes develop that resemble viral hepatitis but serologic test results do not suggest the above illnesses. These patients have a condition currently known as non-A, non-B hepatitis, which is responsible for about 90% of cases of posttransfusion hepatitis and 25% of sporadic cases of hepatitis in the United States. Studies of outbreaks in communities or hospital facilities of many episodes of viral hepatitis in humans and chimpanzees and of repeated inoculations of chimpanzees and marmosets with infectious serum have established the existence of more than one agent responsible for this illness. At least one of the agents appears to be waterborne, spread by the fecal-oral route and does not lead to a carrier state. Current interest in discovering the etiology of non-A, non-B hepatitis is reflected by the many reports identifying agents possibly related to this illness. These include reverse transcriptase activity in plasma products and human serum specimens from cases of posttransfusion hepatitis, 27-nm viruslike particles in stool specimens of Nepalese patients with epidemic non-A, non-B hepatitis and marmosets infected with their serum, a putative antigen by immunocytochemical staining in the liver of a chimpanzee with acute non-A, non-B hepatitis and isolation of an 85- to 90-nm membrane-coated virus from chimpanzee liver cultures inoculated with serum from patients with posttransfusion hepatitis. Other investigators have repeatedly detected hepatitis B viral DNA and hepatitis B surface antigen by radioimmunoassay using monoclonal antibodies in non-A, non-B carrier livers or serum specimens. Whether non-A, non-B infection will eventually prove to be due to any of these agents is still open to independent confirmation of these findings.

Non-A, non-B hepatitis should be looked for in patients with sporadic or posttransfusion acute or chronic hepatitis in whom laboratory tests rule out the viral illness previously mentioned. Other conditions to investigate depend on the clinical setting and may include infections (δ-agent, herpes simplex, syphilis, toxoplasmosis, brucellosis, Q fever), metabolic disorders (Wilson's disease, hemachromatosis, fatty liver), biliary tract disease, hemodynamic insults to the liver, drug-induced liver disease and idiopathic chronic active hepatitis.

The clinical course of non-A, non-B hepatitis is variable and may depend on the nature of the responsible agent, the vehicle or route of administration and host factors not yet characterized. Although most cases of posttransfusion acute non-A, non-B hepatitis are clinically silent, this illness causes as many cases of fulminant hepatitis in the United States as does hepatitis B. Posttransfusion non-A, non-B hepatitis leads to serious chronic liver disease (chronic active hepatitis or cirrhosis) in as many as 60% of cases in some series. Primary hepatocellular carcinoma has been described in patients whose only risk factor appears to be posttransfusion non-A, non-B hepatitis.

It is unclear whether this illness can be prevented by administering immune globulin before or after exposure. In a trial of immune serum globulin (ISG) in 175 patients undergoing a cardiovascular surgical procedure, the incidence of posttransfusion hepatitis in treatment and control groups was the same. In a randomized, placebo-controlled trial of hepatitis B immune globulin (HBIG) and ISG in 279 cardiac operation patients, recipients of either globulin preparation had a lower incidence of icteric non-A, non-B hepatitis (1.1% versus 7.4%) and fewer patients progressed to chronic liver disease (0.5% versus 10%). In a similar trial of ISG in posttransfusion prophylaxis of 2,204 patients, ISG reduced the incidence of icteric hepatitis (0.8% versus 1.8%) but not anicteric cases (7.7% versus 6.9%). The biggest reduction in posttransfusion hepatitis in this study was achieved not by ISG treatment but by the use of noncommercial blood (2 cases in 775 recipients of volunteer blood, both in the ISG group). The results of these trials are not easily compared because the globulin preparations, source of blood transfused and recipi-

ents of blood products were different. The studies taken as a group, however, suggest that the exclusive use of volunteer blood may be the most useful measure to prevent posttransfusion hepatitis. Others have shown that serum alanine aminotransferase (ALT) or anti-hepatitis B core antibody (anti-HBc) testing of blood donors and rejection of blood units with elevated ALT or anti-HBc levels may decrease the incidence of posttransfusion hepatitis in recipients. Whether or not immune globulin administration or any other measure can reduce the incidence of hepatitis after transfusion of volunteer blood with normal ALT levels and absent anti-HBc remains to be proved. To date, blood banks have not adopted a policy of screening for these serologic markers epidemiologically associated with non-A, non-B hepatitis infectivity. A recent randomized, placebo-controlled trial of HBIG versus placebo in hemodialysis patients has shown prevention of non-A, non-B hepatitis during but not after administration of HBIG, suggesting that protection was passive and no active immunization occurred.

Treatment studies in this illness continue to be hampered by the lack of reliable diagnostic tests. An unknown number of cases of posttransfusion non-A, non-B hepatitis have been included in trials of corticosteroids in treating chronic active hepatitis. The proper management of chronic active non-A, non-B hepatitis may include a trial of prednisone if the illness is symptomatic, serum aminotransferase and globulin levels are moderately to greatly elevated and a liver biopsy specimen shows severe active liver disease. At Stanford University Medical Center we are currently enrolling patients in a pilot study of human leukocyte interferon for treating patients with posttransfusion non-A, non-B chronic active hepatitis.

Identifying the agent of non-A, non-B hepatitis and developing reliable diagnostic laboratory tests for its detection will allow rigorous reexamination of the data summarized above. A better understanding of the natural history and transmissibility of non-A, non-B hepatitis will then allow a rational approach to its treatment and prevention.

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New Antibiotics

SEVERAL NEW ANTIBIOTICS entered into clinical practice in 1984 and the role of the third-generation cephalosporins was better defined. Although the latter antibiotics are costly, they have several advantages over first- or second-generation cephalosporins and a very competitive race has ensued between cefotaxime, moxalactam, ceftizoxime, ceftazidime and cefoperazone. These agents are frequently used in the empiric treatment of patients with infections like bacterial sepsis, bacillary meningitis or pneumonia before the cause is identified by laboratory studies. Physicians often substitute these compounds for aminoglycosides such as tobramycin and gentamicin to avoid nephrotoxicity. This is particularly the case in infections such as septicemia and community-acquired pneumonia in immunocompromised patients.

Another new antibiotic is a combination of clavulanic acid with ampicillin. The former compound binds β-lactamases of Gram-positive and Gram-negative bacteria, thus allowing ampicillin to penetrate bacterial cells before it is destroyed. Organisms frequently resistant to ampicillin such as *Staphylococcus aureus, Klebsiella* and other Gram-negative bacilli are now sensitive. This compound is taken orally and can be used in treating complicated outpatient infections. We are also looking with interest at a new class of antibiotics known as the quinolines (pyridonecarboxylic acid compounds) which are derived from nalidixic acid. Such agents include ciprofloxacin, norfloxacin and enoxacin and have a broad range of antibacterial activity against both Gram-positive and Gram-negative bacteria. The bottom line is that a physician who practices primarily in the outpatient arena will have several new compounds effective against complicated infections and that will shorten hospital stays.

The concept of diagnosis-related groups (DRGs) and its inherent logic that dictates reimbursing hospitals is also having an effect on antibiotic prescriptions. Hospitals are looking to their pharmacies to provide tighter guidelines for the use of antibiotics, as they often account for 20% to 30% of all pharmacy purchase costs. New ways are also being developed to treat morbid infections in the outpatient clinical area and thus decrease the duration of hospital stay for patients who have resolving infections such as osteomyelitis, abdominal abscess, pneumonia, empyema and even endocarditis. Infusion centers exist where patients can receive on a daily outpatient basis antibiotics via Hickman lines or catheters in peripheral veins with "heparin locks." Another approach is to employ nurses to visit the homes of patients to administer antibiotics daily. Antibiotic costs will probably gain in importance as a deciding factor in their use.

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Calcium Channel Blockers

CALCIUM CHANNEL BLOCKING agents are important new drugs used in treating coronary and other cardiac diseases. The currently available drugs, diltiazem hydrochloride, nifedipine and verapamil, have been effective in treating coronary artery spasm, and their use in the management of angina and supraventricular arrhythmias has been well documented. The ability of these agents to prevent or relieve spasm theoret-

ically makes them ideal for use in treating other smooth muscle disorders. Although the three available drugs all inhibit the entrance of calcium into cells, they are different compounds and vary in their clinical effect. Nifedipine is a stronger peripheral vasodilator, verapamil causes more myocardial depression and diltiazem and verapamil affect the sinoatrial and atrioventricular nodes. Consideration of these factors is important in choosing which drug will be used, either alone or combined with other drugs such as β-blockers or nitrates.

Several clinical trials have shown the effectiveness of these drugs in treating systemic hypertension, often used as monotherapy. Nifedipine has been extensively studied and may be more beneficial due to its more potent peripheral vasodilating property, and it is very effective in managing cases of hypertensive crisis. Verapamil and diltiazem are also effective in treating hypertension and it is felt by some that they may be more suitable for long-term treatment because nifedipine is more likely to lead to reflex activation of the sympathetic nervous system.

The use of calcium channel blocking drugs in the treatment of pulmonary hypertension is encouraging. All three drugs have reduced pulmonary artery pressure and pulmonary vascular resistance in patients with primary pulmonary hypertension and some types of secondary pulmonary hypertension. However, the response to calcium entry blocking agents in patients with precapillary pulmonary hypertension is unpredictable and the drugs may sometimes produce deleterious effects.

Active clinical investigation is continuing in the use of calcium channel blockers for other conditions, including congestive heart failure, hypertrophic cardiomyopathy, myocardial preservation, bronchial asthma, Raynaud's phenomenon, migraine headache, cerebrovascular spasm, cerebral ischemia, premature labor and disorders of esophageal motility. Calcium channel blockers will likely be increasingly used in smooth muscle disorders, especially as new drugs become available that are more specific for certain types of smooth muscle.

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The Protein C Anticoagulant Pathway and Thrombosis

PROTEINS C AND S are recently discovered vitamin K-dependent proteins that unlike the other vitamin K-dependent clotting factors—II, VII, IX and X—act as physiologic anticoagulants rather than procoagulants. Activated protein C inhibits coagulation by destroying activated factors V and VIII; protein S is an essential cofactor in the expression of protein C's anticoagulant activity. Protein C circulates in an inactive zymogen form and is activated by thrombin bound to an endothelial-cell surface protein, thrombomodulin. Activated protein C may also have a stimulatory effect on fibrinolysis. The protein C anticoagulant pathway thus provides a mechanism whereby formation of thrombin is accompanied by generation of anticoagulant and profibrinolytic activity, limiting fibrin formation to areas of local vascular damage.

Hereditary deficiencies of the protein C anticoagulant mechanism are associated with venous thromboembolic disease. Heterozygous protein C-deficient persons have about half the normal amount of protein C. Many but not all manifest recurrent episodes of thrombophlebitis, pulmonary embolism or both, beginning after the first decade of life, often associated with a precipitating event such as trauma or an operation. Administering heparin or warfarin is effective. Warfarin therapy reduces the levels of all vitamin K-dependent proteins, but protein C levels fall faster than levels of factors II, IX and X. Therefore initiating warfarin therapy, especially with loading doses, may create a brief period of increased vulnerability to thrombosis, including the rare syndrome of dermal thrombosis with necrosis ("warfarin skin necrosis"). Such complications can be avoided by continuing a regimen of heparin for several days, until full oral anticoagulation has occurred.

Homozygous protein C deficiency has been described in several newborns, who have little or no detectable protein C and who show dramatic, life-threatening thrombotic complications, including purpura fulminans, a necrotic dermal thrombotic lesion closely resembling warfarin skin necrosis. Constant protein C repletion with prothrombin complex concentrate is the only effective therapy so far described; however, this therapy is associated with a risk of transmitting hepatitis. Acquired deficiency of protein C is seen in cases of disseminated intravascular coagulation, liver disease, vitamin K deficiency and warfarin therapy; the clinical consequences of such deficiency states are not well established.

A diagnosis of protein C deficiency is best made with one of the recently described functional assays, as normal levels of a functionally defective molecule will not be detected by antigenic assays. Its diagnosis in a patient receiving warfarin requires finding a disproportionately low protein C level when compared with that of another vitamin K-dependent protein, such as factor II, VII or X.

Partial or complete protein S deficiency causes a tendency to venous thromboembolic disease very similar to that of heterozygous protein C deficiency. The use of warfarin or heparin is effective treatment. Neither protein C nor protein S deficiency has been clearly shown to increase the risk of arterial thromboembolism. A search for other defects in the protein C anticoagulant pathway, such as quantitative or qualitative deficiencies of thrombomodulin, is under way in many laboratories and may further increase our understanding of the pathophysiology of thromboembolic disease.

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Antibody Testing for the AIDS Retrovirus—Implications for Clinicians

A NEW HUMAN RETROVIRUS (variously called LAV, HTLV-III or ARV) has been isolated from tissues of patients with acquired immunodeficiency syndrome (AIDS) and with lymphadenopathy in both Europe and the United States. Antibodies against this virus have been detected in a high percentage of AIDS patients, asymptomatic homosexual men and men with hemophilia. Investigations of blood donors implicated as the source of transfusion-acquired AIDS suggest that there may be a prolonged asymptomatic period of infectivity. Testing of all blood donors for antibody to the AIDS retrovirus (ARV) may soon be required. Enzyme-linked immunosorbent assays (ELISA) for ARV antibody will be used to screen blood units and those found to have the antibody will be discarded. This measure appears both practical and reasonable as a means of preventing future cases of transfusion-acquired AIDS.

The availability of this test will create several problems for practicing clinicians. First, positive tests will be found in persons not in any group known to be at risk for AIDS. Many of these ELISA results will be false-positive. Because confirmatory tests such as Western blotting or immunofluorescence are expensive, technically demanding, not widely available and of uncertain sensitivity, it will be difficult initially to determine which positive results reflect possible infectivity for others or an increased risk of AIDS developing. Despite this uncertainty, persons with repeatedly positive tests should be notified because they can take actions to reduce potential spread of the virus via sexual contact, child bearing or nonsexual transfer of body fluids.

The notification of a positive test result will have enormous emotional impact on most persons and requires that physicians be well informed about the limitations of the tests and implications of the results. Even if systems are developed to inform persons of their results through public agencies, many will seek reassurance and follow-up from their personal physicians.

The second problem for clinicians will be the skillful use of these tests for diagnosis. Because of the wide spectrum of clinical manifestations of AIDS-retrovirus infections and the high prevalence of the AIDS-retrovirus antibody in groups at high risk for AIDS, the diagnostic usefulness of finding the antibody in high-risk patients with unusual clinical syndromes will be limited. For example, should a gay man with idiopathic Bell's palsy or thrombocytopenia and a test positive for AIDS-retrovirus antibody be diagnosed as having an ARV-associated condition? While these tests will help to expand knowledge of the clinical spectrum of AIDS-retrovirus infections, they may also be confusing and misleading.

One possible solution to these problems is the development of tests to detect the AIDS virus directly in blood and tissues. This may be accomplished by growing retroviruses in cultures or detecting virus-specific antigens or nucleic acids. These techniques eventually may replace the soon-to-be released antibody assays. In the meantime, physicians will be faced with the difficult task of explaining and interpreting a test of uncertain significance to anxious patients.

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New Antiarrhythmic Agents—Amiodarone, Mexiletine, Tocainide

UNTIL RECENTLY, antiarrhythmic drug therapy has been restricted to a few agents. Over the past decade, however, there has been a dramatic increase in the number of agents that have been or are soon to be released for clinical use. One drug, tocainide, has just been released for clinical use and two others—amiodarone and mexiletine—are subject to intensive clinical investigation.

Amiodarone

Amiodarone, an agent that prolongs myocardial refractoriness in almost all types of cardiac cells, is quite effective in the clinical management of supraventricular and ventricular arrhythmias and arrhythmias associated with the Wolff-Parkinson-White syndrome. In numerous clinical trials amiodarone effectively suppressed these arrhythmias in patients who did not respond to conventional antiarrhythmic drug therapy. There appears to be general agreement that it requires days, sometimes weeks or even, rarely, months for the full antiarrhythmic efficacy of oral administration of amiodarone to become manifest. There still exists some controversy regarding amiodarone's antiarrhythmic efficacy when given intravenously. The drug is most commonly given orally, usually with a loading dose of 800 to 1,800 mg a day during the first week, followed by a daily maintenance dose of 200 to 800 mg a day. Amiodarone seems to be well tolerated by most patients, but with the increasing use of this drug, several unwanted side effects have been recognized. A small percentage ($\leq 10\%$) of patients have to stop taking amiodarone because of more serious and even life-threatening side effects. These include refractory heart failure; pulmonary fibrosis; central nervous system side effects such as tremor, ataxia, paresthesia, headache and nightmare; sinus arrest, and exacerbation of ventricular tachycardia. Less alarming side effects include corneal microdeposits, with possible association of photophobia, thyroid dysfunction (hypothyroidism or hyperthyroidism), a peculiar bluish or slate-gray discoloration of the skin including the face and abnormalities on liver function tests. These complications may take several weeks or even months to disappear after the drug regimen is discontinued. Many investigators, therefore, have suggested that this drug

be used only in patients with serious arrhythmias unresponsive to routine therapy.

Mexiletine

Mexiletine is a structural analog of lidocaine that, however, is effective given orally. The oral dose ranges from 100 to 400 mg every six to eight hours. For urgent therapy, the intravenous route may be considered, with 200 to 250 mg given over five minutes, followed by an infusion of 60 to 90 mg an hour. Mexiletine is effective in suppressing ventricular arrhythmias; its definite role in the control of these arrhythmias, however, is still not defined. Most of the side effects occur during the initial period of therapy and later disappear in most patients during maintenance therapy. These side effects are frequently of central nervous system origin, including tremor, nystagmus, diplopia, dizziness, dysarthria, paresthesia, ataxia and confusion. Gastrointestinal side effects are common and include nausea, vomiting and dyspepsia. Thrombocytopenia and the presence of antinuclear antibody rarely occur but have been reported in some cases. Side effects are more likely to occur at plasma concentrations of greater than 1.5 to 2 μg per ml, which is very close to the therapeutic level. Cardiovascular effects of mexiletine are infrequent and include hypotension, bradycardia and exacerbation of arrhythmias. Mexiletine is generally well tolerated, however.

Tocainide

Tocainide is another structural analog of lidocaine and is, like mexiletine, effective against ventricular arrhythmias when given orally. Both tocainide and mexiletine have relatively long half-lives (12 hours).

In a number of clinical studies, tocainide has decreased the frequency of ventricular premature depolarizations, with variable side effects on ventricular tachycardia. The precise role of tocainide and the clinical setting in which the drug may eventually be used is still not defined. It would appear that tocainide will exert its antiarrhythmic efficacy at plasma concentrations above 6 μg per ml. The oral dosage regimen for tocainide is usually 400 to 600 mg every eight hours. Tocainide is generally well tolerated. Side effects include central nervous system disorders such as tremor, headache, sweating, altered hearing, dizziness, nervousness, hot flashes, paresthesia, blurred vision or diplopia, anxiety and lightheadedness. Gastrointestinal complaints, however, are more common and include anorexia, vomiting, nausea, abdominal pain and constipation.

These three antiarrhythmic agents hold the potential for dramatically increasing a clinician's ability to control serious cardiac arrhythmias. However, with their use comes the additional problem of serious side effects that must be carefully monitored by the physician.

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Clinical Use of Portable Insulin Pumps

AN ARRAY OF evidence supports the view that diabetic complications are attributable to the metabolic derangements caused by elevated blood glucose levels. This concept has been translated to patient care—thus the increased emphasis on blood glucose control. Ideally, changes in blood glucose levels would automatically be sensed and insulin appropriately released into the portal circulation. This could be accomplished with pancreatic islet cell transplantation or by an implantable glucose-controlled ("closed loop") insulin infusion system, a so-called artificial pancreas. While research into these areas continues, the development of blood glucose self-monitoring and patient-controlled external medication infusion pumps permitted clinical trials and now general clinical use of "open-loop" continuous subcutaneous insulin infusion (CSII) systems.

These insulin infusion devices, which use only short-acting insulin, consist of a syringe or an insulin reservoir in conjunction with a battery-operated pump controlled by an electronic mechanism that is designed for a relatively continuous infusion rate of insulin, the basal rate. This basal rate is supplemented by an increase in the insulin infusion rate controlled manually by the patient at mealtimes, the meal bolus. Patients must regularly—at least three to four times a day—monitor capillary blood glucose responses to the insulin infusion to insure adequate insulin doses. The insulin is delivered through disposable plastic tubing and a subcutaneous needle or catheter that is taped in place for one or two days. The newer pumps have alarms for battery failure, overdelivery and high pressure in the outflow system. The larger and nonprogrammable early pumps have been largely replaced by smaller, often preprogrammable devices that are easily concealed and do not interfere with most daily activities. Multiple basal infusion rates can be used for changing activity levels, and meal bolus injections can be adjusted for variable size, quality and timing of meals. These features provide patients with more freedom in their daily lives.

A policy statement from the American Diabetes Association states the primary indication for CSII:

> Failure to achieve an acceptable level of diabetic control in certain type I diabetic subjects with unusual fluctuations in blood glucose levels, despite intensive efforts with proper diet and multiple injections of insulin in single or mixture form and high patient motivation and compliance.

These guidelines include patients who have hyperglycemia associated with elevated glycosylated hemoglobin or patients with frequent hypoglycemic episodes as a result of trying to maintain blood glucose control. Hyperglycemia during pregnancy has been shown to be a definite risk to the fetus, and CSII in this setting can be especially useful for preventing diabetic complications of pregnancy. Some patients with insulin allergies are sensitive to the protamine or

zinc in the insulin preparations. These problems can be eliminated or minimized by infusing short-acting crystalline zinc insulin or, if necessary, a zincfree sodium insulin. Diabetic patients without any of the above indications also have used CSII to obtain more freedom in their life-styles—less restriction in meal timing and easier changing of work shifts or travel. Most patients have an improved sense of well-being when using CSII and they prefer to continue to use it even if blood glucose control has not improved. Possibly this is the result of a psychological effect of being in charge of their disease (the internal locus of control).

Data from our University of California, Irvine, clinic shows no statistically significant improvement in hemoglobin A_{1c} levels during 98 patient-years of CSII use in 46 patients. The mean hemoglobin A_{1c} value for these patients, however, was only mildly elevated (8.4%) before pump therapy and was 8.1% during CSII use.

Three major complications of pump therapy are diabetic ketoacidosis, hypoglycemia and infections at the infusion site—all of which have been associated with mortality. Due to the use of short-acting insulin, ketoacidosis develops rapidly when the insulin infusion is interrupted by tubing occlusion, leakage or mechanical failure of the pump. The accumulation of insulin crystals appears to be the main cause of needle occlusions. Ketoacidosis may be severe before blood glucose levels rise significantly, and patients using CSII may present with "euglycemic" ketoacidosis—that is, severe ketonemia preceding the rise in blood glucose concentrations. Various studies have reported a 2 to 17.5 times increase in the rate of ketoacidosis associated with CSII use. In our clinic the ketoacidosis rate is high before CSII use (0.17 events per year) and remained unchanged after CSII use (0.2 events per year). Although less frequent in these patients, hypoglycemia has occurred due to pump "runaway" and inappropriate insulin dosage through patient or provider error. In our clinic, however, the frequency of serious hypoglycemic episodes (requiring a hospital visit), was reduced from 3.0 events per year before to 0.2 events per year during CSII use and 87% of patients reported a greater than 50% reduction or complete elimination of severe hypoglycemic episodes during CSII use. For patients with ineffective glucose counterregulation, we recommend CSII use but alter our lowest acceptable blood glucose concentrations upward to the 100 to 150 mg per dl range. This treatment has produced remarkable results as described above. Insulin preparations contain antibacterial agents, but the indwelling needle or subcutaneous catheter can be a conduit for local infections when left in one site too long.

Among the solutions to these problems are the use of buffered insulins, appropriate insulin dilutions and daily changing of the infusion set and subcutaneous site with antiseptic care during insertion to avoid occlusions and infections. Patients need detailed instructions and repeated rehearsals to ensure problem-solving ability. Providers who prescribe CSII use should be aware of the possible complications, and an experienced clinician should be available to patients at all times.

The expense of insulin pumps ($1,000 to $2,500 initial costs plus daily supplies) and the requirement for a high degree of patient knowledge, motivation and participation have limited CSII use. Despite these difficulties, an estimated 8,000 to 10,000 insulin pumps are in use in the United States today. It remains to be proved whether the original goal of preventing long-term diabetic complications in large patient populations through sustained normoglycemia can be realized with CSII any more effectively than with multiple subcutaneous insulin injections combined with self-monitoring of blood glucose levels. We view pump use as an alternative insulin administration method that is associated with some serious complications that must be thoroughly considered before being prescribed and used.

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Human T-Cell Leukemia Virus (HTLV)

A VIRAL CAUSE of malignant conditions in humans has long been suspected, although there has been a paucity of confirmatory evidence. Recently, however, an etiologic association has been made between a unique type C retrovirus called human T-cell leukemia virus (HTLV-I), or adult T-cell leukemia virus (ATLV), and an unusual tumor of mature T cells in humans called adult T-cell leukemia/lymphoma. Originally thought to occur only in geographic areas where the virus is endemic, such as southwestern Japan and the Caribbean, the leukemic process has now been identified in other parts of the world, including the southeastern United States, parts of Africa and South America. This suggests that the virus is more widespread than initially thought. The onset of adult T-cell leukemia/lymphoma may be indolent; recently it has been recognized that clinically well patients may have antibodies to HTLV-I for many years before the development of symptomatic disease. The usual presentation of adult T-cell leukemia/lymphoma is abrupt, however, and is characterized clinically by lymphadenopathy, hepatosplenomegaly, skin lesions that may be clinically and pathologically indistinguishable from those of mycosis fungoides, hypercalcemia, lytic bone lesions and interstitial pulmonary infiltrates due either to lymphomatous infiltrates or to opportunistic infections. Involvement of the central nervous system is not uncommon. Malignant cells are found in the peripheral blood of most patients at some time during their course. Treatment usually consists of combination chemotherapy, though responses are generally short-lived, with few patients surviving more than a year.

The malignant virus-infected cells found in the peripheral blood and tissues of patients with adult T-cell leuke-

mia/lymphoma show a great deal of cytologic variation; typically they are medium-sized pleomorphic lymphocytes with lobulated nuclei. The vast majority possess mature T-cell surface markers characteristic of the helper phenotype (OK T4), although, interestingly, they function as suppressor cells.

HTLV infection is exogenously acquired. The mechanism of its transmission is not yet known, but it appears that sexual contact and prolonged exposure are important. Epidemiologic studies show an increased incidence of antibodies against HTLV-I in clinically normal spouses of patients with adult T-cell leukemia/lymphoma. Transmission of the virus has been accomplished in vitro by cocultivating HTLV-positive T-cell lines with normal cord blood or bone marrow T cells; the newly infected cells acquire the nuclear antigens (p19 and p24), specific reverse transcriptase activity and morphologic characteristics of the HTLV-positive T-cell lines. Once this RNA virus has infected the host cell, it replicates using its specific reverse transcriptase and integrates its genetic material into host cellular DNA. The virus is T-cell tropic; its proviral sequence is found within DNA of neoplastic T cells but not within nonneoplastic B cells or somatic cells from the same host. The exact mechanism whereby HTLV causes neoplastic transformation is not known, but it does not appear to carry an *onc* gene.

The human T-cell leukemia/lymphoma virus that is associated with adult T-cell leukemia/lymphoma (HTLV-I) belongs to a family of related T-cell-tropic viruses. HTLV-II has been isolated from the serum of a patient with hairy cell leukemia. HTLV-III has been identified in blood and saliva of patients with the acquired immunodeficiency syndrome (AIDS) and in patients with the AIDS-related complex, including the lymphadenopathy syndrome. Although Koch's postulates have not been fulfilled, it is currently believed that HTLV-III is the cause of these AIDS-related disorders. The discovery of this unique family of retroviruses has provided an important link in our understanding of the pathogenesis of a variety of T-cell disorders.

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Editorials

Female Adolescents With *Chlamydia*

Tomorrow's Candidates for In Vitro Fertilization?

IN THE PAST decade *Chlamydia trachomatis* has been recognized as our most common sexually transmitted pathogen.[1] It is estimated that 3 million chlamydial infections occur each year in the United States.[2,3] Surveys of symptomatic and asymptomatic female populations have identified age and ethnicity as important risk factors for chlamydial infection. For example, a study of seven different family planning clinics in the San Francisco Bay Area found that 16% of adolescent girls seeking birth control advice had chlamydial infection.[4]

The report by Eagar and co-workers in this issue further helps to define the problem. In this study, *C trachomatis* was the most common sexually transmitted disease agent recovered from the screened adolescent girls in all clinic settings, occurring overall at about three times the rate for gonococcal infection. Higher chlamydial infection rates were found for blacks. It is clear that chlamydial infections cross ethnic and socioeconomic boundaries. A higher ratio of chlamydial to gonococcal infection was found in the more economically advantaged white population—as in previous reports.

Chlamydial infection has been reported in as many as 37% of pregnant adolescents.[5] Attack rates for infants with perinatal exposure to *C trachomatis* are about 60% to 70% for any infection, 35% for conjunctivitis and 15% to 20% for the most serious complication, chlamydial pneumonia in infants.[6] Chlamydial infection in infants is preventable. Routine screening of high-risk pregnant women, followed by treatment with erythromycin of those found infected, has been shown to be a cost-effective preventive strategy.[7]

The most important complication of sexually transmitted chlamydial infection is acute salpingitis. Pioneering studies in Sweden, recently confirmed in the United States, have found that approximately one in four patients admitted to hospital with acute salpingitis had upper genital tract infection with *Chlamydia*.[8-10] It is estimated that salpingitis is ten times more likely to develop in a sexually active 15-year-old girl than in her 25-year-old counterpart (1:8 versus 1:80).[9] If one assumes that the infertility rate following a single bout of salpingitis is about 10%, then almost 1% of sexually active teenage girls will become infertile as a result of acute salpingitis each year. Acute salpingitis is a major public health problem, with direct medical costs well in excess of $1 billion each year.[11] Rising rates of ectopic pregnancies and involuntary infertility add to the dreadful toll this disease exacts. The evidence for its role in tubal factor infertility is convincing.[12]

It is imperative that we, as a nation, begin some formal efforts to control this epidemic. The measures suggested by Eagar and colleagues are appropriate: (1) Presumptive therapy is appropriate for conditions where *Chlamydia trachomatis* is known to occur at relatively high rates (endocervicitis, salpingitis, nongonococcal urethritis in men, gonorrhea and other sexually transmitted diseases.[13,14] (2) Routine treatment of sexual contacts is called for. (3) In those settings where high rates of chlamydial infections occur, antibiotics effective against *C trachomatis* should be used whenever possible. (4) High-risk populations should be screened. (5) Greater education concerning the risks and symptoms of chlamydial infection should be provided.

In addition, more effort is needed to educate health care providers as to the importance of chlamydial infections and the guidelines for managing them. The educational efforts must be specifically designed to be appropriate for adolescents and their health care providers. Diagnostic tests must be made more widely available.

Initiation of these steps may help to control chlamydial infection, yet there is an important missing link. Many data have been accumulated on the importance and prevalence of chlamydial infection in women because they routinely have pelvic examinations. Similar data are not available for men unless they are symptomatic or named contacts. If 15% to 20% of sexually active girls have chlamydial infection, what percentage of sexually active adolescent boys must also be carrying this organism? Without noninvasive screening methods for detecting asymptomatic infections in men, we can never hope to generate this type of information. Recent studies have stressed the prevalence of asymptomatic urethral infection in men.[15] Unfortunately, without reducing the youthful male reservoir, we shall never really control chlamydial (or gonococcal) infections. Preliminary studies suggest that evaluation of pyuria in first-catch urine specimens may have a high predictive value for urethral infection in adolescent boys.[16] If a urine specimen could be used for screening and diagnostic tests, a noninvasive tool for identifying the asymptomatic male reservoir may evolve.

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Medicine in the Fabric of Society

IT IS NOW increasingly evident that medicine has become an integral part of modern society, particularly in America. The health care enterprise, taken as a whole, is one of the largest industries in the nation, and within it medicine plays a seminal role. But, in addition, in one way or another medicine has come to influence or be influenced by almost every facet of today's society. In this sense medicine is becoming an increasingly important part of what might be called the fabric of society. Why is this happening, and what is its meaning for physicians and the medical profession as a whole?

There may be at least three reasons why medicine is beginning to be so interwoven with a changing society. First, many of the great advances in medical science and technology not only affect the way physicians practice but have also begun to create significant ethical, social, economic and political problems with which society as a whole must now deal in one way or another. Second, modern society, with its growing social, economic, political and, above all, technologic complexity and interdependence, is itself creating all kinds of new problems for medicine and health care that require new responses by physicians and the medical profession. And third, modern society is after all a human society, made up of humans whose behavior and responses are genetically as well as experientially determined, and who for better or worse are individually unique and must react within the framework of their biologic nature to all the stresses of the increasingly complex world in which we all live. Medicine is the professional discipline that deals with human adjustment or maladjustment to the stresses in the internal and external environments of the individual persons who in the aggregate make up modern society. If the stresses are manageable and adjustment is adequate, then health and well-being prevail, but when this is not the case symptoms of stress or frank ill health appear in individual persons or in groups of people. Physicians and the medical profession, therefore, find themselves promoting health and wellness wherever possible, and where there is unhealth they proceed with the diagnosis, treatment and correction of whatever maladjustment is impairing health whether in the internal or external environment, or both. So, modern society being what it is, medicine is coming to pervade much of its fabric.

What then should medicine be in today's society? Or, put another way, what *is* medicine in today's society?

- Medicine is *personal*—and *biological*. Adjustment and maladjustment in health and illness are very individual and very personal, and the mechanisms of adjustment and maladjustment are fundamentally biological in the broadest sense of human nature and human behavior.
- Medicine is *professional*. Physicians have been set somewhat apart by society, and given special training and special privileges to serve their patients and the public. As professionals, physicians have set their own professional standards for their training and practice. This may be considered by some as elitist, but clearly it can be no other way.
- Medicine is *science and technology*. Its science and technology probe deeply into the nature and causes of illness, injury and emotional disorders, and the findings are applied to the promotion of health and well being, to prevention of ill health, to diagnosis and treatment to repair damage to the mind and body when ill health occurs and to restoring adequate adjustment to stress whether from a person's internal or external environment.
- Medicine is *art*. There is more to medicine than science and technology. The science is not exact and may never be. Furthermore, every person, whether sick or well, is unique, genetically and experientially different from everyone else. Medicine therefore has to be a human, caring relationship between doctor and patient (or the profession and the public, for that matter), with the art being to orchestrate the personal, cultural, scientific, technologic, social and economic factors that must be harmonized if there is to be health or if an unhealthy state is to be corrected in an individual or in the environment (society).
- Medicine is *social*. It is part of every known culture. The modern health-care enterprise is a complex social system, so far only poorly studied or understood. Social issues, growing out of the technical capabilities of modern medicine, are calling into question many of society's ways of doing things. In many ways medicine is actually a social science with much of this science yet to be developed.
- Medicine is *economics*. Medicine has become a significant part of the economics of modern society, and the economics of modern society has become a significant part of medical practice. Health care is a good product but it is costly. Medical economics is presently at center stage in health care and of much concern to both medicine and society.
- Medicine is *politics*. Medicine has been political in this country for more than a century. Its power has been, and still is, rooted in what is recognized as its competence in matters of health and health care. Now there is formidable competition in the political arena of health care. Medicine and health care have become everybody's business. The politics of medicine will not go away, and medicine badly needs a more identifiable constituency and a more positive program if it is to become truly effective politically.

There can be little doubt that the thread of medicine weaves through the fabric of today's society. It is not yet clear how strong this thread will be or just who will weave its pattern in the fabric. Will the pattern be decided by society? Probably so. But who will create the design? There is an enormous opportunity to weave (1) the underlying biology of human nature and human behavior, (2) the science, technology and art of medicine and (3) the social, economic and political realities of health and health care into a creative pattern in the fabric now being woven for the complex and interdependent society that is emerging in America today. An unanswered question is, does American medicine have the interest, the wherewithal or the resolve to be and be recognized as "physician to society," and in this role bring its skills to bear to help diagnose and treat the all-too-evident maladjustments in health and health care in this nation?

MSMW

Case Reports

Computed Tomographic Findings in Orbital *Mucor*

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MUCORMYCOSIS is an increasingly important infection in immunocompromised patients; knowledge regarding the variability of its clinical manifestations is expanding steadily.[1] The infection is of paranasal sinus origin and may involve the orbit secondarily via freely communicating foramina and venous channels.[2] Death often ensues when the infection spreads either into the cavernous sinus or the central nervous system.

Early diagnosis of rhinocerebral mucormycosis is crucial for a successful outcome.[3] Computed tomographic (CT) scanning is used to visualize many intraorbital pathologic abnormalities. The patient discussed in this paper had extensive orbital *Mucor* that appeared minimal on a CT scan. This inability of the scan to reflect the severity of infection prompted our review of the literature describing the use of CT scans for detecting this potentially fatal, opportunistic infection. The search showed that a disparity between scan findings and the severity of the disease is the rule rather than the exception. Recognition of this disparity has significant implications for appropriate diagnosis and management of orbital *Mucor*.

Report of a Case

A 62-year-old woman with agnogenic myeloid metaplasia had been treated with prednisone (20 mg per day) for two years, until she was referred for management of persistent bilateral pulmonary infiltrates. She presented to a community hospital with fever, rigors, shortness of breath and cough. A chest roentgenogram showed a left upper lobe infiltrate. Cultures of blood, sputum and a bronchoscopic biopsy specimen, however, were negative. The patient deteriorated clinically. Culture of an open lung biopsy specimen failed to show a causative agent and empiric therapy with broad-spectrum antibiotics was begun. Subsequently, a severe cutaneous eruption developed, presumably a reaction to the drugs, and her steroid dose was increased fivefold. At this time, she was transferred to Harbor/University of California, Los Angeles (UCLA), Medical Center.

On admission, antibiotic therapy was discontinued and the steroid dose was tapered. The patient's condition improved until the seventh hospital day when right-sided chemosis, proptosis and ophthalmoplegia developed over four to six hours. Within 24 hours there was complete loss of vision, of pupillary reflexes and of facial sensation on the right. Minimal ethmoid mucosal thickening was seen on plain sinus radiographs. A CT scan of the orbits done on the same day (Figure 1) showed thickening of the ethmoid sinus mucosa: the sphenoid sinus was clear. No bone destruction was evident, though there were proptosis of the globe and swelling of the medial rectus. Contrast enhancement was seen around the cavernous sinus but cavernous sinus thrombosis was ruled out by venography. The orbital apex was of normal density and no mass lesions were present. Broad-spectrum antimicrobial and amphotericin B therapy was initiated.

Because the patient's condition continued to deteriorate, the orbit and ethmoid sinuses were explored surgically. Although the tissues looked normal, biopsy specimens taken from the ethmoid mucosa and medial rectus muscle showed characteristic hyphae of *Mucor*. An orbital exenteration and partial maxillectomy were done; extensive retroorbital avascular necrosis and destruction of the orbit by the invading organisms were found. Despite a dosage of 3 grams of amphotericin B given over subsequent weeks, intracerebral extension of the infection developed, to which the patient succumbed.

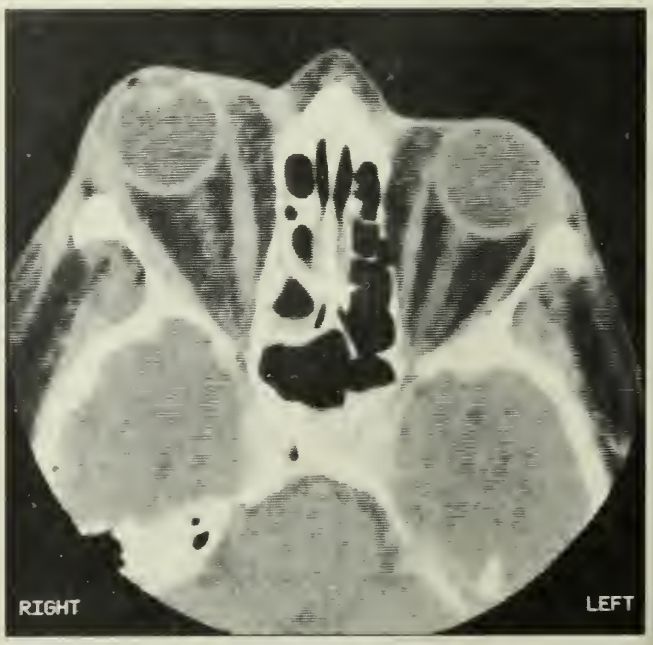

Figure 1.—A computed tomographic scan showing mild opacification of the ethmoids, proptosis of the globe and thickening of the medial rectus muscle on the right. Note absence of bone involvement or evidence of a retroorbital mass or displacement of retroorbital structures.

(Greenberg MR, Lippman SM, Grinnell VS, et al: Computed tomographic findings in orbital *Mucor*. West J Med 1985 Jul; 143:102-103)

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Discussion

Computed tomography of the orbit was first described in 1974. Since then it has been used extensively to visualize intraorbital trauma, tumors and bacterial infection.[4-8] Descriptions of the findings in patients with intraorbital *Mucor*, however, are limited.[9-12] Most reports are restricted to single cases. In two of these single-patient case reports, the CT scan showed evidence of proptosis and medial rectus thickening,[9,10] and one patient was reported to have thickening and displacement of the medial rectus, increased density of the orbital fat and venous engorgement.[11] In all of these individual case reports, there was evidence of extensive sinus opacification on the CT scan.

The only series of cases has been compiled by Centano and co-workers, who reported the cranial CT scan findings of ten patients with rhinocerebral *Mucor*.[12] Extraorbital findings of proptosis (present in half the cases) and sinus mucosal abnormalities (present in seven patients) were common. Pleuridirectional tomography was more sensitive in detecting bony involvement of the sinuses (three patients) than CT scan (one patient). Extensive intraorbital abnormalities were not commonly seen by CT scan; four patients had no intraorbital abnormalities and three had only lateral displacement of the medial rectus. Only three of the patients had an increased density of the orbital apex consistent with an inflammatory mass.

In the scan of our patient (Figure 1), there was mild opacification of the ethmoids and thickening of the medial rectus muscle. Both the optic nerve and orbital apex were normal, however, and there was no bone involvement. The medial rectus thickening was similar to the previously described cases and apparently is a consistent finding. This muscular thickening may represent the earliest finding in orbital *Mucor*. It is a nonspecific sign, however, and the most common CT finding in cases of orbital pseudotumor.

We conclude from both our experience with this patient and from reviewing the English language literature that CT scan findings in orbital *Mucor* may be surprisingly minimal in the presence of advanced disease. Anticipated findings of a retroorbital mass with displacement of retroorbital structures and findings suggestive of massive tissue destruction are not necessarily typical CT findings and their absence should not delay an aggressive pursuit of the diagnosis of orbital *Mucor*.

Addendum

Two additional CT scan findings in cases of orbital *Mucor* have been reported: Kilpatrick and co-workers have described nonenhancement of the superior ophthalmic artery and vein,[13] and Anderson and colleagues have reported widening of the pterygomaxillary fissure.[14]

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Tuberculous Peritonitis Developing in a Case of Documented Peritoneal Carcinomatosis

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TUBERCULOUS PERITONITIS is an uncommon disease, particularly in the United States.[1] However, the rarity of this condition does not diminish the necessity of correctly making the diagnosis as therapy can be curative, whereas the disease left untreated is frequently fatal.[1-4] In this report, the case of a patient with histologically documented peritoneal spread of gastric carcinoma in whom tuberculous peritonitis developed is presented to emphasize the difficulty and importance of making this diagnosis in the presence of intra-abdominal malignancy.

Report of a Case

A 32-year-old Japanese woman presented to the UCSD (University of California, San Diego) Cancer Center for consideration of experimental intraperitoneal chemotherapy for gastric carcinoma. One year earlier she had had a subtotal gastrectomy for adenocarcinoma of the stomach. Four months before being seen at our institution, an umbilical mass was noted that on biopsy proved to be adenocarcinoma. Three months later an abdominal wall mass was detected. The patient had an exploratory laparotomy, which showed numerous peritoneal implants on the serosal surface of the small and large bowel and on the surface of the liver. A biopsy specimen (reviewed by several pathologists) confirmed the presence of recurrent tumor. A Tenckhoff catheter was placed and a regimen of experimental intraperitoneal chemotherapy of cisplatin, cytarabine and doxorubicin hydrochloride was begun.[5] Corticosteroids were included in the antiemetic regimen used. Ascites was noted on an ultrasound examination done to assist in catheter placement. At the time of initiating therapy, a left upper lobe pulmonary nodule not seen on previous chest x-ray

(Markman M: Tuberculous peritonitis developing in a case of documented peritoneal carcinomatosis. West J Med 1985 Jul; 143:103-105)

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ABBREVIATIONS USED IN TEXT

BCG = bacille Calmette Guérin
CT = computed tomographic
PPD = purified protein derivative

films was noted and, because the physicians caring for the patient initially suspected the nodule to represent metastatic gastric cancer, no further diagnostic evaluation was undertaken to rule out other causes of the lesion. Specifically, sputum specimens for culture were not obtained and a skin test for tuberculosis was not applied. The chest x-ray film also showed biapical scarring consistent with old granulomatous disease. The patient's maximal temperature in hospital was less than 38°C and she said she did not have respiratory tract symptoms. Peritoneal fluid cell counts, protein values and cytologic findings are shown in Table 1.

A month later the solitary pulmonary nodule had enlarged substantially. The patient remained afebrile but had lost weight and had increased ascites. A specimen of a transbronchial biopsy done to document the presence of metastatic disease showed only chronic inflammatory cells. Washings were negative for mycobacteria on acid-fast bacillus stain. Cultures of specimens obtained at the time of bronchoscopy eventually showed no growth of *Mycobacterium tuberculosis*. A purified protein derivative (PPD) skin test was done that was positive despite the fact that the patient was intermittently receiving steroids as antiemetic agents. A second course of intraperitoneal chemotherapy was administered.

Three months after presenting to our institution, the patient remained afebrile but her appetite was poor and her weight had fallen 10 kg (22 lb). An abdominal computed tomographic (CT) scan showed a pronounced increase in ascites compared with an earlier study, with probable peritoneal implants on the bowel and peritoneum. A percutaneous lung biopsy specimen again showed only inflammatory cells. However, specimens of both the biopsy material and the peritoneal fluid grew *M tuberculosis*. Unfortunately, before an antituberculous regimen was started, a small bowel obstruction developed. She underwent a bypass procedure to relieve the obstruction when conservative measures failed. At the operation the bowel was completely matted together by extensive adhesions. A biopsy specimen of material believed to represent tumor showed extensive necrotizing granulomatous inflammation without evidence of tumor. Postoperatively the patient was placed on a regimen of triple-drug antituberculous therapy. Following a slow postoperative recovery, she was able to eat normally and recovered her lost weight. She continues to receive antituberculous therapy and, except for intermittent abdominal pain most probably due to extensive adhesions, the patient remains clinically stable and without evidence of recurrent cancer 18 months following documentation of widespread peritoneal carcinomatosis.

Discussion

Tuberculosis developing in association with neoplastic disease is a well-recognized clinical problem. In a series of patients from a large cancer hospital, 9 of 1,646 patients with adenocarcinoma of the stomach seen between 1950 and 1981 were found to have tuberculosis at some time during the course of their disease—an incidence of 55/10,000 patients at risk.[6] In none of these patients was tuberculous peritonitis stated to have developed and the difficulty of diagnosing tuberculosis in this clinical setting was not commented upon.

TABLE 1.—*Peritoneal Fluid Analysis*

Date	Total Leukocyte Count/μl	Differential Count (%) Segmented Forms	Lympho-cytes	Mono-cytes	Protein Grams/dl	Cytol-ogy
Presentation . .	9,800	30	56	14	5.9	Neg
1 mo*	685	3	56	41	. . .	Neg
3 mo	150	1	93	6	6.0	Neg

Neg = No malignant cells seen

*Months following presentation to the UCSD Medical Center, San Diego.

Our patient had several predisposing factors to the development of active tuberculosis. First, she was born in Japan and had only recently moved to the United States. The incidence of tuberculosis is presently ten times higher in Japan than in the United States.[7] Second, the patient had had a subtotal gastrectomy for gastric cancer. This procedure increases the risk for the subsequent development of tuberculosis, most probably due to malnutrition.[6,8] Third, the patient was treated with chemotherapeutic agents and steroids, which are immunosuppressive. Steroids, in particular, have been implicated in the high rate of tuberculosis associated with lymphoreticular malignancy.[6,9]

The signs and symptoms of tuberculous peritonitis and peritoneal carcinomatosis are almost identical.[10] Both are associated with exudative ascites, weight loss, pain and abdominal masses.[1-4,11-17] While fever is more likely to be associated with infection, in cases of tuberculous peritonitis fever may be absent[1,3,4,11,15-17] and it is common for cancer patients (particularly those with liver metastasis) to have low-grade fevers. The finding of predominantly mononuclear cells in the ascitic fluid (Table 1) should suggest the possibility of tuberculous infection even if cultures are negative.[1,2,11,17] One report suggests a significantly higher rate of culture positivity if at least 1 liter of ascites fluid is cultured rather than the small volume (less than 100 ml) normally obtained during a diagnostic paracentesis.[2]

While the finding of a positive PPD skin test in a patient such as the one in this report should raise a strong suspicion for the presence of *M tuberculosis*, a major portion of the population of Japan has been exposed to this agent, and a positive PPD cannot be equated with the presence of active disease.[7] Also, in an immunocompromised host, a negative PPD skin test does not exclude the presence of tuberculosis as the patient may be anergic. Therefore, several skin tests should be applied when evaluating immunocompromised patients (steroid therapy or cancer) for the presence of tuberculosis.

Recently, it has been suggested that the CT scan may be helpful in the differential diagnosis of tuberculous peritonitis,[18] but the radiographic findings are relatively nonspecific and in our patient suggested progressive intra-abdominal tumor. The finding of an enlarging pulmonary nodule in a patient with known intra-abdominal malignancy would suggest the presence of metastatic tumor. However, cavitation of the lesion or rapid growth (as in this case) should raise the suspicion of an infectious cause.

The importance of correctly diagnosing tuberculous infection, particularly in patients with concomitant malignant le-

sions, is more than of academic interest and cannot be overemphasized. The disease, even in its advanced form, is curable with appropriate antituberculous medications, but the success of therapy improves when it is instituted early.[16] In a patient in whom tuberculosis is even considered in the differential diagnosis, it is imperative that cultures be adequately done to rule out this diagnostic possibility. Any biopsy specimens obtained in such patients (transbronchial, peritoneal, bone marrow) should be sent to a microbiology laboratory with specific instructions to culture for *M tuberculosis*.

At the time of exploratory laparotomy, a large biopsy specimen failed to show histologic evidence of tumor. While this finding could certainly represent sampling error or a dramatic response to the intraperitoneal chemotherapy, gastric cancer is only modestly sensitive to the currently available agents and complete remissions are extremely rare.[19] In addition, even in patients responding to therapy, an 18-plus month survival from the time of diagnosis of an extensive intra-abdominal metastatic tumor with no current evidence of active disease is very unusual.

Two retrospective analyses of patients with lung cancer undergoing surgical resection showed improved survival for those patients in whom a postoperative empyema developed.[20,21] It was speculated that the nonspecific immune response induced by the infection resulted in tumor cell kill and an increased survival rate. In a rat transplantable tumor model, it has been found that the intrapleural injection of bacille Calmette Guérin (BCG) vaccine can suppress tumor growth.[22] Similarly, while the benefit of intrapleural administration of BCG following curative surgical treatment of lung cancer remains controversial,[23] one group has shown a small but statistically significant improvement in survival for patients with stage I non-small cell lung cancer receiving intrapleural BCG plus isoniazid compared with a control group receiving only isoniazid.[24,25] No benefit could be shown for patients with stage II or III lung cancer in this study. It is interesting to speculate that the intensive inflammatory response elicited by the *Mycobacterium* infection shown at the operation may have resulted in significant tumor cell kill and be responsible for the patient's remarkable clinical course.

In summary, this case emphasizes the similar clinical and laboratory features of peritoneal carcinomatosis and tuberculous peritonitis. A high index of suspicion for the latter disease was finally responsible for the correct diagnosis being made and appropriate therapy being instituted. In addition, this case underscores the importance of strongly considering in the differential diagnosis of a complex case treatable diseases, especially when the alternative explanations have limited therapeutic implications.

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Granuloma Inguinale in a White Teenager—A Diagnosis Easily Forgotten, Poorly Pursued

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THE CONDITION variously known as granuloma inguinale, donovanosis or granuloma venereum is an uncommon disease process producing genital ulcerations that can be quite locally destructive and are known for their chronicity. The disease is most commonly seen in the southeastern United States. Although it is mandatory that this venereal disease be reported to the health department, many physicians are unaware of this fact, which may lead to underreporting. It is a relatively rare disease in California (Table 1). Granuloma inguinale can be easily diagnosed, although sometimes it is overlooked in differential diagnosis because of its rarity. The purpose of this report is to present a case of granuloma inguinale occurring in a white teenaged girl from California who suffered from a

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TABLE 1.—*Reported Cases of Granuloma Inguinale, 1977-1982**

Area	1977	1978	1979	1980	1981	1982
United States	75	72	76	51	66	17
Region 9 (Ariz, Calif, Hawaii, Nev)	4	2	1	2	4	5
California	4	2	1	2	4	4
Atlanta	36	41	47	25	4	0

*Source Form CDC 73.688, p 20, Centers for Disease Control, Atlanta. (Provided courtesy of Perry Brown, Director of Public Health, Epidemiology Analyst, Department of Health Services, County of Los Angeles.)

chronic ulcerative vulvar lesion for several months before the condition was diagnosed as granuloma inguinale. We also review the clinical manifestations, diagnostic techniques and therapeutic regimens related to granuloma inguinale.

Report of a Case

The patient, an 18-year-old nulligravida woman, presented to the University of California, Los Angeles (UCLA), with a ten-month history of painful vulvar ulceration. She had been sexually active for two years. The first sexual partner had been a "casual contact" some weeks before she had begun a steady relationship with her current sexual partner of 11 months' duration. The first partner had traveled to New Orleans before their sexual contact.

The patient had an ulcer that started as a very sore, small spot in the left vulvar area beginning ten months before the examination. She noted dysuria, increased vaginal discharge and local itching and went to see the first of eight physicians. Specimens from the patient were cultured for gonorrhea, herpes and routine culture and sensitivity several times over the subsequent ten months. These tests, including five separate serologic tests for syphilis (VDRL), were negative. During this ten-month period the patient took courses of antibiotics, usually for only a week, including ampicillin, doxycycline hyclate (Vibra-Tabs), erythromycin and cephalexin (Keflex). A course of amoxicillin and cefaclor (Ceclor) was also taken. After some of these therapies there was a waning of the ulcerative lesion; the ulcer returned persistently, however. The patient's current sexual partner was examined by a physician and was told that he had no lesions or disease. Despite the vulvar ulceration, the patient would intermittently have coitus when the ulcer was "almost healed." After sexual activity the ulcer would at times exacerbate, and the patient's physician felt that this activity was causing local trauma leading to the problem. When the patient came to the UCLA Vulvovaginitis Clinic, she had not been taking antibiotics for three weeks. The ulceration was being treated by local measures such as sitz baths and was becoming increasingly painful.

On physical examination, including vital signs, the following abnormalities were found. A mildly tender left inguinal adenopathy was noted. There was a 2 by 2.5 cm, exquisitely tender, soft ulceration involving the left labium majus and perineal body (Figure 1). The ulceration had a well-defined border and appeared to have superficial infection and local induration with hypertrophic granulation tissue at the edges. There were no lesions on bimanual examination and inspection of the cervix, vagina and rectum.

Laboratory tests (UCLA Clinical Laboratories) disclosed the following values: A leukocyte count of 10,600 per μl, a differential of 65% segmented forms, 6% band cells, 4% eosinophils, 1% basophils, 18% lymphocytes and 6% monocytes; hematocrit was 43.1%. Urine culture and sensitivity were negative. Tissue specimen cultures were negative for *Hemophilus ducreyi*,[1] *Neisseria gonorrhoeae* and herpes virus[2]; culture of the ulcer bed was positive for penicillin-resistant *Staphylococcus aureus*; VDRL was negative. A wet mount of a specimen from the lesion for dark-field examination was negative for *Treponema pallidum*. A "touch preparation" of the ulcer was *positive by Giemsa stain for Donovan bodies* (Figure 2). A vulvar biopsy specimen showed chronic and acute ulceration without evidence of viral cytopathic effect.

Because of an allergy to tetracycline, the patient was treated with chloramphenicol, 50 mg per kg per day, divided in four doses every six hours. After seven days of this treatment, the ulcer responded by a 30% decrease in size, less induration and pain and evidence of healing by reepithelialization with no secondary infection. Antibiotic therapy was continued and the patient was monitored frequently. After 23 days of a regimen of oral antibiotics, the ulcer had completely reepithelialized, but there was moderate residual scarring (Figure 3).

Following this ordeal the patient requested and was referred for psychological therapy with regard to her future sexuality. It was noted that she was showing substantial depression and had negative feelings concerning future sexual relationships and sexual functioning after this chronic illness.

Discussion

The first case of granuloma inguinale was reported in the United States in 1913,[3] although the earliest description of the disease came from India in 1882.[4] In the early 1900s, Don-

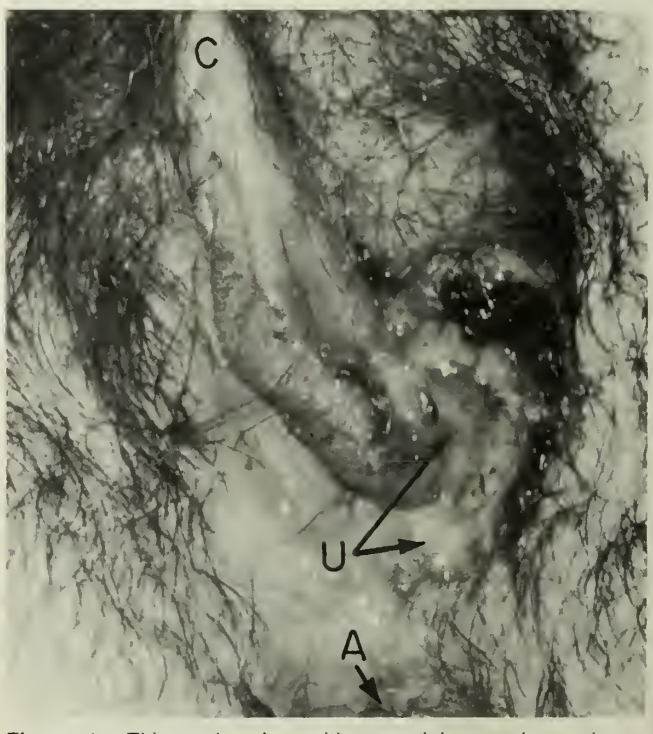

Figure 1.—This tender ulcer with a serpiginous edge and surrounding induration was photographed during the patient's first visit. **A** = anus, **C** = clitoris, **U** = ulcer of granuloma inguinale

ovan described the agents that he suspected caused this disease, referring to them as "epithelial cell parasites" due to intracellular protozoa,[5] thus the term donovanosis, which today is used preferentially as the identifying nomenclature in some articles. The term "granuloma inguinale" is attributed to Crocker in his treatise on tropical diseases of the skin.[6] The bacterial cause of this disease was not established until the early 1940s. Even today Koch's postulates have not been satisfied in determining the precise cause or mechanism of the disease process.[7]

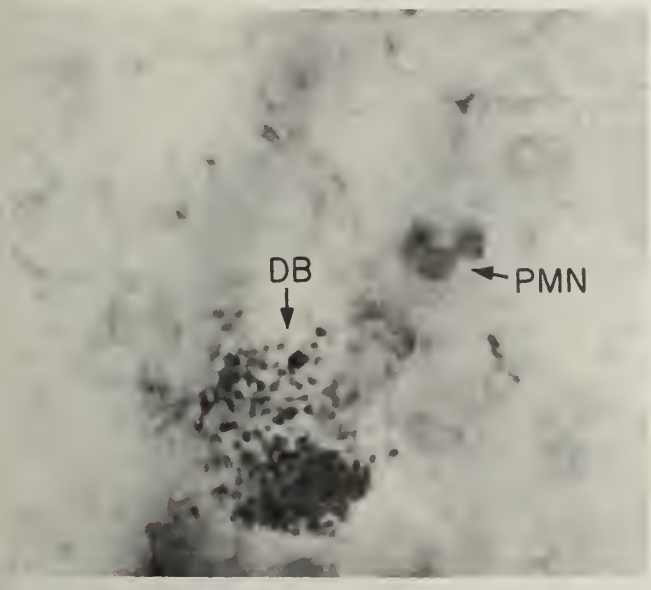

Figure 2.—Oil-immersion microscopy of the touch preparation of the ulceration, Wright's-Giemsa preparation, showed numerous histiocytes laden with Donovan bodies, an example shown here **(DB)** next to a polymorphonuclear leukocyte **(PMN)** (reduced from magnification ×2,500).

Figure 3.—Reepithelialization of the ulcer was evident four weeks after initiation of antibiotic therapy. **RU** = reepithelialized ulcer, **V** = vagina

Calymmatobacterium granulomatis, the Donovan bodies and presumed causative agents, was first cultured in the yolk sac of chick embryonated eggs,[8] defining a bacteriologic cause for granuloma inguinale. The yolk sac remains the most reliable culture mechanism. Although not available for clinical use because of the difficulty of cultivation, adaptation of yolk sac preparations to semisynthetic media has been successful,[9] with best growth in an anaerobic to microaerophilic environment. This bacterium has been studied ultrastructurally with electron microscopy[10] and is now classified as a nonmotile, encapsulated, pleomorphic, Gram-negative bacillus. Although sexual contact has been postulated as the most common method of acquiring the disease, it has occurred in people who are not sexually active. Transmission is unpredictable because there is a low incidence of infectivity in sexual partners of infected patients,[11] as cited in our case report. The disease is more common in the southeastern United States, in underdeveloped countries, in dark-skinned populations and in men.[12]

The incubation period varies from days to months.[13] The initial lesion, a papule, breaks down and becomes a beefy-red, granulomatous ulcer after a varying length of time. Unless secondary infection occurs, the ulcers are minimally painful; secondary infection increases pain greatly, however. The chronicity of the disease is its hallmark. In women, lesions are found most commonly in the labial or perineal areas. Vaginal and cervical lesions associated with abnormal genital bleeding have been reported.[14] A vesicovaginal fistula may also occur. In men, severe disease may erode and destroy the penis. In affected homosexual men, there is a high percentage of perianal involvement.[10] Secondary infection is common in lesions of women. Ulcerations are superficial with an irregular serpiginous edge and surrounding induration and have central hypertrophic granulation tissue. Dissemination of these lesions and death have been reported, but rarely.

Because tissue culturing techniques are not generally available, the diagnosis of granuloma inguinale is usually made using standard techniques that are more readily available throughout the United States.[15] The touch preparation technique involves either touching a glass slide to the granulation tissue of the lesion or preferably obtaining a small piece of tissue through biopsy and crushing the tissue between slides, then processing the slides either with Giemsa, Wright's or Leishman's stains. This permits identification of histiocytes laden with intracytoplasmic organisms (Donovan bodies). If the patient has been treated for a significant amount of time before, it may be necessary to repeat the process more than once to identify the agent. The organisms cease to exist in the lesion bed, at least by the above techniques, after a patient has had 5 to 14 days of tetracycline therapy.[10] Although serologic testing for this particular disease has been reported, it is not now clinically used.[12]

A longer-than-usual course of antibiotics is necessary to cure the disease compared with other typical venereal disease conditions. As seen in this case, despite several therapeutic regimens that included drugs stated to be effective against the disease, short courses of treatment may be ineffective. Tetracycline,[16] co-trimoxazole[17] and chloramphenicol[18] are effective against this disease. Streptomycin sulfate[19] has long been

considered an efficacious agent for the disease, but because of the problem of the route of administration, potential resistance and side effects, the oral agents are preferable. Penicillin is not effective and ampicillin[10,20] elicits variable and, at times, poor response. Because the drugs discussed above are contraindicated in pregnancy, erythromycin[21] is the current drug of choice, possibly with the addition of lincomycin.[22] No double-blind controlled studies testing the efficacy of treatment have been reported. Regardless of which agent is used, the usual week to ten-day course of antibiotics used in other types of bacterial infection does not seem long enough to eradicate granuloma inguinale, especially in its chronic form. Observation during treatment, extension of treatment until Donovan bodies are no longer identified on Giemsa touch preparations and a duration of treatment for at least three weeks give a high degree of success. Attempts at surgical excision should be avoided because the potential for spread of the infection exists and ultimate resolution with antibiotic treatment can be expected.

In the case of the patient we discuss, who was seen by eight physicians, only the last physician briefly entertained the diagnosis of granuloma inguinale and sent the patient immediately to a referral center for confirmation. There the diagnosis was made in short order with a touch preparation and the disease was treated effectively. Had treatment continued without diagnosis of this uncommon disorder, quite possibly the patient would have suffered extensive tissue destruction, requiring surgical reconstruction. The delay in diagnosis and successive unsuccessful courses of treatment over a prolonged period may be considered contributing factors leading to the request for psychotherapy regarding sexual dysfunction. Granuloma inguinale is a reportable disease of suspected venereal transmission; thus the case was reported to the public health department for follow-up.

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Postoperative Small Bowel Intussusception

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ALTHOUGH RARE in adults, postoperative small bowel intussusception can account for as high as 16% of cases of intussusception in children.[1] Frequently the diagnosis of postoperative intussusception is delayed because the clinical manifestations are masked by a recent abdominal procedure and an inappropriately low index of suspicion for this diagnosis.

We recently treated three patients with postoperative intussusception, which cases illustrate the problems in making the diagnosis and the usual clinical presentation following intra-abdominal operations in children.

Reports of Cases

Case 1

The patient, a 9½-month-old female infant, was admitted to a regional hospital with a three-week history of intermittent fever, vomiting and diarrhea and constipation during the previous few days. On admission the temperature was 37.5°C (99.5°F). The abdomen was distended with hypoactive bowel sounds. Abdominal rebound tenderness or muscular guarding was not present. The remainder of the physical examination showed no abnormalities. The serum chloride level was 111 and carbon dioxide level 20 mEq per liter; the rest of the electrolyte values, a complete blood count and analysis of urine were normal. Roentgenograms of the chest were normal, but abdominal films showed dilated loops of small and large intestine. The admitting diagnosis was large bowel obstruction and an exploratory celiotomy was done. Both small and large bowel were dilated, but a mechanical obstruction could not be found. An incidental appendectomy was done. The postoperative period was complicated by persistent ileus and wound dehiscence presumably due to infection. Following surgical treatment of the wound dehiscence, the temperature remained elevated to 38°C to 39°C (100°F to 102°F). On the fourth postoperative day bowel function returned and the nasogastric tube was removed. A regimen of metoclopramide hydrochloride was begun for treatment of persistent abdominal distension. On the fifth postoperative day a bloody stool was passed and she was referred to our institution for further management.

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Upon admission she was dehydrated and the rectal temperature was 37.6°C (99.7°F). The abdomen was distended, tympanic and tender to palpation. The digital rectal examination showed pinkish mucus that was Hemoccult positive. The leukocyte count was 14,400 per μl with 47% segmented neutrophils, 8% band neutrophils, 33% lymphocytes and 12% monocytes. Except for a low serum chloride level, the rest of the laboratory values were within normal limits. The abdominal roentgenograms showed several dilated loops of small intestine with air-fluid levels consistent with intestinal obstruction (Figure 1). A barium examination of the colon showed an ileoileal intussusception (Figure 2) that was subsequently confirmed during a diagnostic celiotomy. The intussusception was located about 12 cm proximal to the ileocecal valve and about 15 cm of ileum was involved. There was obvious intestinal necrosis requiring resection and enteroenterostomy. The postoperative course was benign and she was discharged on the eighth postoperative day.

Case 2

The patient, a 7-month-old male infant with Hirschsprung's disease, was admitted for a Duhamel pull-through procedure. The diagnosis of rectosigmoid Hirschsprung's disease was made when he presented at 5 days of age with toxic megacolon treated by emergency colostomy.

On admission the infant weighed 9.5 kg. Results of physical examination were normal except for the presence of a sigmoid colostomy. A complete blood count, serum electrolyte values and results of a urinalysis were within normal limits. The operation was carried out without difficulty, but postoperatively there was a persistent ileus. On the fourth postoperative day bowel sounds were heard, though his abdomen remained distended. Roentgenography of the abdomen showed dilated loops of small bowel with air-fluid levels consistent with either a postoperative ileus or a mechanical obstruction. The serum electrolyte values remained within normal limits. A trial of nasogastric suctioning and intravenous fluid replacement for two days failed to resolve the obstruction and an abdominal exploration was carried out. An ileoileal intussusception was found. Although the involved intestine was edematous, there was no evidence of necrosis. Manual reduction of the intussusception was accomplished and the postoperative course was uncomplicated.

Case 3

A 9-month-old female infant with Hirschsprung's disease was admitted for a Duhamel pull-through procedure. The patient had a diverting transverse colostomy at the age of 2 months when Hirschsprung's disease was diagnosed. The physical examination on admission showed no abnormalities except for the presence of the colostomy. The complete blood count, serum electrolyte levels and results of a urinalysis were within normal limits.

Following adequate bowel preparation, closure of the colostomy and a Duhamel pull-through procedure were done without complications. On the third postoperative day flatus was passed and oral feedings were begun. On the fifth postoperative day emesis occurred and the abdomen became progressively distended and slightly tender to palpation. Bowel sounds were hypoactive and no masses were palpated. The serum electrolyte values remained normal. Roentgenography of the abdomen showed dilated loops of small bowel consistent with mechanical obstruction. A small bowel intussusception was suspected and she underwent abdominal exploration when this diagnosis was confirmed. It was possible to manually reduce the ileoileal intussusception. The remaining postoperative course was uncomplicated.

Figure 1.—An upright roentgenogram of the abdomen shows dilated loops of small intestine and air-fluid levels.

Figure 2.—Barium enema showing a dilated ileum proximal to a coil-spring mass consistent with an ileoileal intussusception. The diagnosis was confirmed at an operation.

Discussion

Postoperative small bowel intussusception is the second most common cause of intussusception in children and it accounts for from 5% to 10% of cases of postoperative small bowel obstruction.[1] It shows an equal distribution between boys and girls.[2] Frequently, it occurs following retroperitoneal or long abdominal operations, but it has also been reported following minor procedures such as appendectomy, lymph node biopsy or herniorrhaphy.[2,3]

Two thirds of the cases of postoperative intussusception reported in the literature became symptomatic within the first week and 90% became symptomatic within the first two weeks following a surgical procedure.[2] This was also observed in our cases. In the infant in case 3, symptoms developed following a transient episode of what appeared to be normal bowel function; this has also been previously noted.[2]

Awareness of this disorder is the most important factor in making the correct diagnosis. Unfortunately, the symptoms and signs are not obvious as they are frequently masked by the clinical manifestations of a recent abdominal surgical procedure. The classic symptoms and signs of spontaneous intussusception such as abdominal pain, the presence of a palpable mass and hematochezia are usually absent.[2]

A delay in the diagnosis can lead to serious complications and death.[2] Case 1 illustrates the complications of delayed treatment—segmental intestinal necrosis necessitating resection of the involved ileum. Although a barium examination of the colon was diagnostic in this patient, it is most often not helpful. Frequently the small bowel intussusception is sufficiently proximal to the ileocecal valve that adequate evaluation is not possible. In some patients with a competent ileocecal valve, no evaluation of the small bowel is possible. Finally, in patients who have had a recent colonic operation, a barium enema would be contraindicated.

The etiology of postoperative intussusception remains unknown. Several factors have been implicated, such as disordered motility and edema following a surgical procedure, local hypoxia, anesthetic agents, electrolyte disturbance and medications (particularly cancer chemotherapeutic agents).[1,2] In postoperative intussusception, a specific lead point has been reported in only about 8% of the cases.[2] A lead point was not identified in any of our patients.

Awareness of postoperative small bowel intussusception in children should lead to prompt diagnosis and avoidance of the potentially high morbidity and possible mortality. Although a barium enema study has infrequently been a useful diagnostic tool, prompt surgical exploration remains the best diagnostic and therapeutic approach.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Immunization for Measles

TO THE EDITOR: In "Measles Transmission in Medical Facilities"[1] in the March issue, Drs Dales and Kizer recommend "routine immunization of new medical facility staff members born since 1956 . . . who lack documentation of prior immunization or disease," because "serologic surveys in California have indicated that, currently, perhaps 10% to 15% of young adults (ages 18 to 22 years) are susceptible to measles." This would apply where there is a lack of an immunization record showing month and year of immunization or where the diagnosis of measles was not made by a physician. I question the need for that recommendation, because more than 90% of those who will be subjected to immunization are already immune.

In the prevaccine era, more than 90% of all Seattle area measles cases occurred among children under the age of 9 and the median age was 5.5. There were large measles epidemics in the 1966-67 and the 1968-69 measles epidemiologic years and lesser outbreaks occurred in later years. Live virus vaccine was extensively introduced through a school immunization program in the fall of 1967 and the program was carried out subsequently for several years. In the 1970s and 1980s, passage of state immunization requirements resulted in immunization of many susceptibles who had slipped through earlier plus the reimmunization of many children who could not adequately document previous immunization.

Would it not be more cost effective and equally efficacious to focus their recommendation upon areas where measles cases have been introduced and accept an adult's statement that he or she has had the disease and the vaccine? Most diagnoses of measles cases were not called to the attention of a physician during the years when measles was epidemic and persons over the age of 22 are unlikely to have any immunization records to prove that they were immunized. Moreover, at least half of the physician-diagnosed measles cases during the recent postvaccine era have proved to be wrong.

In the example cited, it should be noted that in 64% of the cases the patients were of school age or younger and most of them had not been previously immunized. Had they been, the outbreak might also have stopped before ten generations. There is a good chance that it would have stopped at one or two generations.[2,3]

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Upright KUB Roentgenogram

TO THE EDITOR: I am one of the authors of the article "Spontaneous Colonic Drainage—A Rare Complication of an Amebic Liver Abscess" that appeared in the February issue.[1] I would like to correct a typographical error in one of the figures.

On page 254, Figure 2, right picture, the caption reads "Another upright chest roentgenogram taken immediately after the episode of diarrhea." The caption should read "An upright KUB roentgenogram taken immediately after the episode of diarrhea."

Please bring this correction to the attention of your readers.

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REFERENCE

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Holmesian Skills in Medicine

TO THE EDITOR: My imagination was captured by Sherlock Holmes when I was a child. It was a joyful occasion when in medical school an esteemed professor led me in a Holmesian exercise in observation and deduction at the bedside. At that moment medicine became fun. Since that time, I have carried the same exercise to generations of medical students. We spend two minutes at the bedside in the intensive care unit, no touching or talking allowed. We then go out of sight of the patient and deduce the case history—which is always possible if the instructor uses his or her own powers of observation in choosing a patient. Most of my students react as I did.

"The faculty of deduction is certainly contagious." The reason for its contagion lies in the joy of seeing that which one might easily have overlooked and the power of deducing important conclusions from an instantly available fact. The charm of Sherlock Holmes is the joy he derived from making obvious that which to others was obscure. He made joy out of discipline where others made only drudgery.

There is accomplishment in mastering medical discipline, to give a complex medical presentation through to the last detail of a system review without omitting a significant detail. But there is joy in observing (as opposed to seeing, of course) the body language that says that a patient is getting well, or the small sign that makes a difficult decision easy. The disci-

pline to stand at a bedside keeping one's eyes busy and mind on the sensory input has become one of the lost arts. It's a pity, because the joy goes with it. On the other hand, there is no reason why those skills cannot be developed in a home study program. It is a skill that the best clinicians have, and I am pleased that Dr Miller has detailed the Holmesian connection.[1]

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1. Miller L: Sherlock Holmes's methods of deductive reasoning applied to medical diagnostics (Commentary). West J Med 1985 Mar; 142:413-414

* * *

TO THE EDITOR: Contrary to popular belief,[1] the extraordinary gift of Sherlock Holmes was not his ability to deduce (to reason from general theories to particular facts), but to induce (to reason from facts to theories). Compared with his ability to induce, Holmes's ability to deduce was quite ordinary. For example, given the general premise that all unicorns have a single horn, Holmes—and the average 10-year-old child—could readily deduce that any particular unicorn has a single horn.

The ability for induction is characteristic of skilled medical diagnosticians, but medical diagnosis also entails deduction and observation. Consider the logical sequence of evaluating a patient:

A set of diagnostic possibilities—the differential diagnosis—is generated by induction from observed facts. From each potential diagnosis, additional findings are predicted by deduction. Then, the predictions are tested against observed data (for example, laboratory results or response to treatment) to support or rule out the diagnosis.

The distinction between deduction and induction is profound; it is equivalent to the difference between hindsight and foresight. Because he wrote with hindsight, Conan Doyle sprinkled clues he had deduced after the fact; clues contrived to perplex readers who—together with real detectives and physicians—must experience mysteries with foresight. Holmes, on the other hand, enjoyed the same perspective as Conan Doyle, without which his successful inductions were no more than lucky guesses; the data he induced from can be explained by any number of alternative hypotheses.

Because deduction can be probative but induction can prove nothing, physicians have long sought deductive methods of diagnosis; for example, collecting enough data to be conclusive and seeking pathognomonic signs. These wished-for methods are based on the premise that diagnostic categories can be completely defined as a collection of their known elements. However, disregarding identities (such as a tiny head equals microcephaly), completely defined categories and pathognomonic signs are merely imaginary products of inadequate knowledge.

In the ideal universe of scientific taxonomy, diagnostic categories comprise all facts pertaining to an illness—whether the facts are known or not. In the real world of clinical medicine, however, the known diagnostic categories cannot be more complete than the set of known facts—a set that is not only incomplete, but partially incorrect as well. In former days, for example, bizarre behavior, delusions and disordered thinking were diagnostic of witchery, but contemporary knowledge and diagnostic theories do not accommodate witchery. Similarly, contemporary diagnostic categories will be replaced, expanded, narrowed or deleted in the future because of enhanced knowledge and more sophisticated theories.

The belief in deductive methods of diagnosis encourages physicians to act as mere technicians—that is, as if findings dictate treatment with no need for diagnosis. Thus, if a person is delusional, chlorpromazine is indicated. If after treatment the person remains delusional, more chlorpromazine is indicated. The technician is blind to alternative diagnoses such as bipolar illness or drug toxicity.

Physicians cannot practice competent medicine by applying Holmes's fictional methods of diagnosis; they must recognize that both induction and deduction are needed for adequate medical assessment and treatment. Those physicians who abandon the logical foundations of their profession are charlatans, because their "science" is fictitious. Certainly, charlatans cannot reverse today's politically expedient trend of corrupting medical facilities into fix-it shops.

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1. Miller L: Sherlock Holmes's methods of deductive reasoning applied to medical diagnostics (Commentary). West J Med 1985 Mar; 142:413-414

How Important Is Knowing It All?

TO THE EDITOR: As a primary care physician working in specialties (emergency medicine and family practice) that have considerable overlap with other specialties with regard to relevant medical knowledge, I do not feel the findings of Kronlund and Phillips[1] published in the April issue are very surprising. Neither are they necessarily much reflection on the competence of the physicians surveyed. They rather reflect the explosion in data relevant to the practice of medicine. I am sure this in large measure explains the increasing specialization and subspecialization of physicians. The practice of clinical medicine is usually not conceptually difficult, but human memory is simply not up to the task of "knowing it all" with the certainty required for the safe practice of medicine. Furthermore, the unique and creative aspects of human intellect (reason, assimilation, hypothesizing) are wasted in trying to do so. *Roundsmanship* too often passes for good judgment and replaces practicing the art of medicine compassionately.

I see widespread use of accessible and easy-to-use clinical computer data bases as a powerful means to free physician energy for thinking and assimilating, rather than memorizing. Such an approach will also be a major factor in alleviating one major source of residency stress—the perceived need to know it all—alluded to elsewhere in the same *WJM* April 1985 issue.[2,3] Paradoxically, I would probably end up having more facts at my finger tips using an easily accessible computer data base. At the moment I needed to know some fact and was, therefore, most interested and curious, I could ask the computer and instantly have the data sought. Consider this situation as opposed to being bogged down by the lengthy and sometimes fruitless searches of textbooks we all do, or simply cannot take the time to do, when we need to, during a busy clinic day. Too often the question is not answered, and the chance to learn and improve is lost. What is needed is a rapid,

easy-to-use data base. But it is unnecessary and unrealistic to expect it to be located in each physician's head, except pertaining to a relatively narrow specialty area.

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A Treatment for Enuresis

To the Editor: I have been interested in the subject of enuresis for many years and have come up with the following observation and recommendation for treatment. I have observed the simple fact that the more one exercises and perspires the less one urinates. This is because in a sense the skin organ has function much like the kidneys, in that it also excretes liquid, not unlike urine.

Bearing these simple conclusions in mind, I have recommended that the enuretic person engage in continuous rhythm exercise, such as running, cycling, swimming or even walking briskly for one hour daily, preferably in the late afternoon, without replacement of fluids thereafter.

Barring the presence of infection or a congenital malfunction, I have been quite pleased with the results. In addition to this diuretic effort of the exercise program, the patients gain many fringe benefits of exercise which include a better feeling about themselves. This seems to help the patients as well.

I would be interested in other practitioners' comments on this simple treatment of enuresis.

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Hitting Below the Belt

To the Editor: Since the House of Delegates of the American Medical Association passed a strong resolution for a ban on boxing, the pros and cons of such a move have made it not only to the front page but also to the editorial page.

The media, not often given to throwing bouquets to the AMA, were almost embarrassingly complimentary. Editorials spoke of the courage and the foresight of the doctors in taking this stand.

Medical associations from New York to California joined in the plea for a total ban on boxing. Even Howard Cosell now wants boxing banned!

It seemed that only those who would suffer a financial loss—the promoters, the boxing associations, the TV moguls—were willing to come out swinging against such a ban.

There were a few bleeding hearts who wept that by banning boxing we would be depriving young men from the minorities of a chance at the "big money."

Along with the public endorsement of a ban on boxing came the admission that it had little or no chance of being put into effect. A great idea but—because the average American man (and some women) seems to get a psychological lift out of sitting in front of the tube, beer in hand, watching one human wreak violence on another—a total ban will never come to pass.

There is one hope, one simple remedy, that has so far received little attention and has been mentioned only in passing by *JAMA*: total banning of blows to the head.

Simple as that.

We all know there is a ban on hitting a boxing opponent below the belt. One punch beneath the belt will bring a strong warning from the referee. A second or third may bring disqualification of the offending boxer.

Now, all men who have participated in contact sports have at one time or another experienced a blow to the gonads, and we well remember that the pain was excruciating. But it was temporary and our genitalia suffered no long-lasting injury, either to our sex drive or to our reproductive capacity.

Why then is hitting below the belt considered such a heinous act, when rendering repeated blows to the brain, an uppercut to the chin or a sharp left to the head is considered an expert exhibition of the fine art of boxing?

Hitting below the belt can give temporary pain, but repetitive blows to the head, from the Adam's apple up, can produce contusions, lacerations and hemorrhages from the brain stem to the gray matter. And it has been shown that this occurs even when protective headgear is used.

The quick-witted, physically superb Muhammad Ali, with his dancing feet, has been hailed as the greatest boxer of all time. More likely his legacy to tomorrow's generation will be a newly identified clinical entity—"pugilistic parkinsonism," a damaged brain syndrome characterized by a shuffling gait, glazed eyes and dull-witted mumbling speech.

A call for a total ban on boxing may, indeed, be a noble but futile gesture. But if hitting below the belt is so wrong, then certainly it is time for all physicians to cry out that repeatedly banging the brain of another human with the fist is gross, vicious violence.

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Vietnamese Patients and Physicians

To the Editor: I have read, with interest, the article "Culture Shock—A Review of Vietnamese Culture and Its Concept of Health and Disease" by Dr Nguyen, published in the March issue.[1]

Being a Vietnamese physician myself, I would like to share some personal thoughts in regard to the treatment of Vietnamese patients. I sincerely feel that Vietnamese physicians would be most helpful to their compatriots by guiding them into the American values and way of life. I do not think "East is East, and West is West." Many of the basic human values are shared by ancient Oriental culture and American culture.

The Vietnamese should make an effort to erase their misplaced pride, and realize that there may be better ways than theirs. For example, it is erroneous to identify being late to appointments as a less stressful way of conducting business. Likewise, they should begin to ask what they could do to give back to America in return for all the goodness they have received from her. Respect is to be earned, not asked for. The Vietnamese will not earn respect by asking for special status because of being refugees.

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Topics in Primary Care Medicine

How to Help Your Patients Function Better

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Most physicians who care for patients with chronic illnesses attempt to help them be as active, sociable and productive as possible. Yet the traditional history, physical examination and differential diagnosis are inadequate for assessing the full range of common health-related problems in chronically ill patients. Such patients, during periods when their medical condition is stable, are frequently most concerned about problems of physical, psychological or social functioning.

Quickly assessing how well a patient is functioning can be difficult in clinical practice. Patients with the same disease often function quite differently. One patient with rheumatoid arthritis might be restricted to the home and require considerable assistance eating, bathing and dressing, while another, with equally severe disease, might be an active member of the community and need only minimal help. The severity of the disease might be described by a patient's sedimentation rate, inflamed joint count or treadmill exercise results. Ability to function, however, should be described by a patient's capacity to carry out a broad range of usual daily activities, such as housekeeping and family or social life. In this paper we suggest how physicians might identify, manage and treat limitations of physical, psychological or social function.

Detecting Functional Limitations

No standardized method for detecting a patient's functional limitations currently exists. Usually, a concerned physician asks patients directly about their problems or about their usual daily activities. Some functional limitations may be obvious or quickly elicited, but the full extent of disability is often hidden. Comprehensively assessing function requires thorough inquiry, which takes time and may not always be feasible. A brief, systematically validated self- or family-administered questionnaire is therefore an ideal substitute for direct inquiry in many circumstances. A valid survey of functional status, like a laboratory test, can be used to compare one patient's abilities with others and the same patient's progress over time.

Several functional assessment questionnaires are available. Unfortunately, some are too long for general office use. Others are specifically designed for the elderly or are limited to a single aspect of function. We are currently testing a brief, comprehensive, functional assessment questionnaire* that is suitable for any English-speaking patient. Over the next decade, we expect that many such questionnaires will be developed to suit the needs of practitioners in a variety of settings.

Clarifying Problems of Physical, Psychological or Social Function

Suppose a review of a patient's performance on a functional status survey revealed the following limitations:

- Difficulty with using transportation,
- Trouble with taking care of the home,
- Very few social activities,
- No sexual relationships.

Suppose further that the patient (a woman) says that she has not had sexual relationships for 20 years but is not concerned about it, and that what really bothers her is difficulty

*This questionnaire is available from the authors upon request.

(Rubenstein LV, Calkins DR, Fink A, et al: How to help your patients function better [Topics in Primary Care Medicine]. West J Med 1985 Jul; 143:114-117)

From the Department of Medicine, UCLA Center for the Health Sciences, Los Angeles (Drs Rubenstein, Fink, Young, Kosecoff, Davies and Brook), and the Department of Medicine, Beth Israel Hospital, Harvard Medical School, Boston (Drs Calkins, Cleary, Jette and Delbanco).

This research was supported by the Robert Wood Johnson Foundation. The views expressed herein are those of the authors and not necessarily those of the Foundation.

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using a bus because, without transportation, she is unable to take part in social and community activities.

This patient's chief functional limitation is "difficulty with transportation," to which a physician's typical response might be to send her immediately to a social worker. A more effective response, however, would be to analyze the problem more carefully before deciding what to do about it. When the action of using the bus is divided into its component parts, the patient's problem can be defined more specifically and becomes amenable to solution.

Action . . .
Using the bus.
Basic Components . . .
Get dressed and ready to go.
Walk to the bus.
Climb onto the bus.
Pay bus fare.

The patient's major difficulty can be with any one of these components, and each suggests a different solution. In some cases, a change in medications may be the answer. (Is the patient so drowsy that she has difficulty getting ready to go?) In others, a social work consultation, an exercise program or behavior modification may be appropriate.

Setting Priorities Among Multiple Problems

As illustrated in the previous example, patients with chronic illness may have many functional limitations at the same time. Improvement is most likely when patients and physicians agree about the importance of a symptom or problem. Sometimes just showing a patient the list of problems identified on a questionnaire and asking which are most important will reveal a patient's priorities. Other questions that can give a physician a sense of which problems the patient may be motivated to solve include:

- What is the one thing you would most like to be able to do, but cannot now do because of your health?
- Under what circumstances in your daily life does your health bother you most?
- What activities would you most like to participate in if your health were better?

Addressing important and more easily solved problems early in the relationship can build a patient's confidence.

Managing Limitations

Once an analysis of a patient's functional limitations has been made, the most efficacious management strategy can be selected.

1. *If the problem is caused by physical impairments or organic disease,* then medications, an operation, physical therapy, exercises, mechanical aids or prostheses (such as those prescribed by physical and occupational therapists) would all be considered. Consider two patients with treatable disease:

Patient 1
Chief problem:
Difficulty with sexual relationships.
Etiology:
Evaluation reveals erectile dysfunction due to primary testicular failure and endogenous depression.
Treatment:
He is treated with a regimen of antidepressants and testosterone injections.

Patient 2
Chief problem:
Difficulty walking short distances.
Etiology:
Angina pectoris, "controlled" by self-imposed restrictions on activity and a maximal drug regimen. No evidence of major depression or of poor compliance.
Treatment:
She is treated with a coronary artery bypass graft procedure.

2. *If the problem is primarily caused by social stress,* treatment usually consists of teaching the patient to cope with or alter the social environment. This may include obtaining financial aid or social support. Treatment might also include helping the patient deal with the effects of changes in her or his functional status on disability payments or on other family members. Consider two patients whose problems were caused primarily by social stress:

Patient 1
Chief problem:
Difficulty with sexual relationships.
Etiology:
Despite testosterone therapy, this patient continues to have erectile dysfunction on intercourse (he now has spontaneous erections). Marital stress due to a live-in mother-in-law is diagnosed.
Treatment:
Treatment consists of finding a nearby board-and-care facility for the mother-in-law and encouraging the wife's brother to participate more in his mother's care.

Patient 2
Chief problem:
Difficulty walking short distances.
Etiology:
Despite a coronary artery bypass operation, this patient is unable to increase her exercise. The problem appears to be due to fear of walking alone in her high-crime neighborhood.
Treatment:
Treatment consists of finding a younger companion to walk with patient.

3. *If the problem is caused primarily by psychological stress,* treatment usually requires development of a therapeutic alliance between doctor and patient through which a patient can gain insight into his or her personality and learn ways of coping. Below are two examples of functional problems related primarily to psychological stress.

Patient 1
Chief problem:
Difficulty with sexual relationships.
Etiology:
This patient has a long history of being unable to sustain long-term relationships. He has spontaneous erections and can have intercourse under certain circumstances.
Treatment:
Treatment consists of first providing insight as to the psychological nature of the patient's complaint—such as discussing the patient's prior history of unsatisfying relationships and the reasons for thinking that psychiatric intervention could be beneficial—and then referral to a psychiatrist.

Patient 2
Chief problem:
Difficulty walking short distances.
Etiology:
This patient had a cardiac operation three months ago and now is incapacitated by anxiety. She feels that she may "come apart" with any movement and is unresponsive to reassurance or taking mild tranquilizers. On questioning, she relates that her father died postoperatively when she was 5 years old.
Treatment:
Treatment consists of further exploring her feelings. Once she has reexamined her childhood experience, she can focus on the ways in which her current situation is different from it.

How to Set Goals

Getting patients to improve function often requires that they change specific behaviors. People are most likely to change when they are active participants in setting goals and practicing new behaviors.

In the medical setting, it is useful to distinguish between two kinds of goals: those to improve functional ability and those to prevent and treat disease. Functional improvement goals should be based primarily on a patient's expectations, such as taking a trip to Hawaii, getting training for a technical job or doing volunteer work. Goals for treating disease usually require substantial input from the physician. For example, a chronically depressed, obese patient with physical, psychological and social disabilities might tell her physician that she wanted to support herself designing and producing toys (a functional- rather than disease-related goal). She and her physician might, in addition, share the goal that she lose 100 lb over the next two years, a treatment goal that may indirectly affect functioning. These two goals need not be met simultaneously. It is often beneficial with a patient of this kind to emphasize the goal of functional improvement and to temporarily ignore the weight-loss goal. As the patient becomes involved and motivated, weight loss may be easier to achieve. Even if she does not lose weight, this patient could become a more cheerful, engaged person, an important achievement in its own right.

To be useful, goals must be specific. To set specific goals, the physician often has to ask the patient to use very precise words. The following examples illustrate this process:

Vague:
To get out more.
More specific:
To go to the movies.
Vague:
To get a job.
More specific:
To take the technical training course for a clerical job.

To increase the patient's chances of achieving a goal, it helps to include a standard of performance for each goal, as in the example below.

Goal:
To go to the movies.
Standard:
To go to the movies at least once a week.
Goal:
To take the technical training course for a clerical job.
Standard:
To pass all three parts of the course.

How to Change Behavior

In addition to setting goals, physicians may want to explore ways of establishing and reinforcing a specific behavior through stimulus control, positive or negative reinforcement, demonstration and practice.

Stimulus Control

Sometimes problem behaviors persist because they have become part of a routine, as in the following.

Problem:
Unable to walk to the bus.
Diagnosis:
Shortness of breath due to smoking and chronic obstructive pulmonary disease.
Dysfunctional behavior:
Smokes when anxious.
Behavioral treatment:
Teach relaxation techniques to use at onset of anxiety.

Positive Reinforcement

The positive reinforcement resulting from functioning better will ultimately be the most important means of motivating most patients. But specifically rewarding appropriate behaviors can be helpful. It is important to ask patients what they will find reinforcing; verbal praise or positive feedback can be reinforcement enough, but the use of rewards chosen by a patient and self-administered can also be helpful. Rewards of this kind might include nominal sums of money, a vacation or a new dress or suit. Two examples of how this process can work are given below:

Patient 1
Chief problem:
Difficulty with sexual relationships.
Diagnosis:
When the patient's physician reviews his symptom diary, it seems clear that the patient's attempts at intercourse with his wife are accompanied by frustration and criticism on her part.
Treatment:
The wife's help is enlisted to give positive reinforcement for mutual pleasurable touching of limbs and face, progressing over the succeeding weeks toward intercourse.

Patient 2
Chief problem:
Inability to walk short distances.
Diagnosis:
This patient had a cardiac operation three months ago, and is unable to resume walking despite excellent cardiac test results. Careful behavior analysis reveals that whenever the patient begins to improve her walking, she feels she must also begin strenuous housework.
Treatment:
Treatment consists of forbidding housework temporarily, while instituting a program of weekly trips to the movies if she succeeds in increasing her exercise.

Negative Reinforcement

Negative reinforcement and punishment are used to suppress undesired behaviors. Ignoring an outburst from a patient is considered negatively reinforcing, whereas speaking sternly to a patient who should quit smoking can be a form of punishment. Punishing patients is often ineffective and may have undesirable side effects. They may, for example, go to another physician.

Demonstration

Demonstration, combined with supervised practice of the desired behavior by the patient, can be a valuable tool. The "see one, do one, teach one" model by which physicians traditionally learn medical procedures is a good example of an active learning process based on demonstration. When demonstration and practice are combined with a written description of what to do, preferably accompanied by illustrations, the chances of patient success are maximized. For example:

Problem:
Decreased work performance.
Diagnosis:
Job stress due to unrealistic work goals.
Dysfunctional behavior:
Unable to say no to boss.
Behavioral treatment:
Physician and patient act as boss and employee. The patient practices

saying no when the physician-boss makes unrealistic demands, such as working during evenings when the patient is taking classes.

Problem:
Unable to walk to the bus.
Diagnosis:
Difficulty walking.
Dysfunctional behavior:
Not using cane properly.
Behavioral treatment:
Demonstration and practice of proper cane technique.

Problem:
Unable to walk to the bus.
Diagnosis:
Difficulty walking due to dyspnea.
Dysfunctional behavior:
Not using inhaler to control asthma symptoms.
Behavioral treatment:
Demonstration and practice of proper inhaler use.

Summary

The traditional history and physical examination provide only limited information about problems of physical, psychological and social function. Furthermore, traditional therapeutic techniques are not designed to foster full patient participation in improving functional status. The methods of detection, diagnosis and treatment of functional limitations discussed in this article were developed to meet the needs of the ever-increasing population of patients with chronic illnesses, among whom limitations of functioning have major long-term effects. We realize that we may be proposing an increase in the amount of time spent with each chronically ill patient. We also expect, however, that using these methods will increase the effectiveness of many physicians who are interested in devoting attention to improving patients' function. We expect that success will depend on a patient's willingness to participate, resources and a physician's ability to use our suggestions.

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Special Article

Medi-Cal Hospital Contracting—Did It Achieve Its Legislative Objectives?

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The 1982 Medi-Cal reforms and reductions established selective contracting with hospitals for inpatient care of Medi-Cal beneficiaries. The legislation established a special negotiator and criteria to be used in selecting contract hospitals. We report the findings of a study that analyzed the characteristics of contract and noncontract hospitals in Los Angeles County to assess how well these criteria were reflected in the outcome of the contracting process. We examine issues of beneficiary access to general inpatient care and to specialized services, the efficiency of contract hospitals compared with noncontract ones and quality-related issues.

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In 1982, Medi-Cal (California's medicaid program) was an obvious target for state legislators who were looking for ways to reduce the state's expected $2 billion deficit. In fiscal year 1981-1982, Medi-Cal expenditures amounted to $4.8 billion, about $1 in every $8 of state expenditures, of which 57% came from state sources and 43% represented the federal contribution. Furthermore, costs were rising rapidly. Between fiscal years 1975-1976 and 1981-1982, Medi-Cal expenditures increased nearly $2 billion, with cost per service contributing 58% of the increase and number of eligible persons adding 11% to the expenditure increase.[1] Faced with these problems, leaders in the legislature—with strong support from the governor and business, labor and insurance industry groups—enacted a series of bills despite objections from the hospital industry and the medical profession.[2]

Among the far-reaching cutbacks and reforms included in Assembly Bill 799, Assembly Bill 3480, and Senate Bill 2012, probably the most significant reform was the decision to selectively contract with hospitals for inpatient care provided to Medi-Cal recipients. The objective of selective contracting was to encourage hospitals to engage in price competition for a share of the Medi-Cal business. A special negotiator was to be appointed, with unusual authority to set negotiating procedures and to conclude contracts with hospitals that would reimburse them on any basis except the old cost-based, fee-for-service system. Once this process was concluded, inpatient care to Medi-Cal recipients would be restricted to those hospitals that had signed contracts. Exceptions would be made for emergency care, care in children's and other specialized hospitals, "crossover" patients (those with Medicare and Medi-Cal) and members of prepaid health plans.

In this article we examine the results of the Medi-Cal selective contracting process with hospitals in Los Angeles County. Variables or characteristics that distinguish contract from noncontract hospitals are analyzed to assess the extent to which criteria established by the legislature were achieved in the outcome of the contracting.

Medi-Cal Hospital Contracting

The special negotiator was fully responsible for negotiating the rates, terms and conditions of the contracts. The legislation exempted the contracts from review and approval by state oversight agencies normally required for contracting services. However, the legislature mandated nine factors, in addition to price, to be considered in negotiating contracts: (1) beneficiary access; (2) utilization controls; (3) ability to render quality services efficiently and economically; (4) demonstrated ability to provide or arrange needed special services; (5) protection against fraud and abuse; (6) any other factor that would reduce costs, promote access or enhance the quality of care; (7) the capacity to provide a given tertiary service, such as specialized children's services, on a regional basis; (8) recognition of the variations in severity of illness and complexity of care, and (9) existing labor-management collective-bargaining agreements.

William Guy, former president of Blue Cross Association of Southern California, was named special negotiator and was

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ABBREVIATIONS USED IN TEXT

ADC = average daily census of patients
AFDC = Aid to Families With Dependent Children
CHFC = California Health Facilities Commission
FTE = full-time equivalent employees
HFPA = Health Facilities Planning Area
NICU = neonatal intensive care unit
PSRO = Professional Standard Review Organization

soon dubbed the "Czar" because of his broad powers. In order to implement the process quickly, Guy chose to reimburse hospitals with a flat per diem rate. He also initially insisted that the contract terms remain secret as provided by the legislation. The secrecy provision, however, prevents the public from knowing even retrospectively a hospital's bid price, the final contract price or the provisions of the contract. Secrecy also makes it difficult for the public or researchers to assess how effectively the Czar fulfilled the legislated criteria to be used in hospital contracting.

Despite the secrecy surrounding the bid prices and the negotiated per diem rates, it is widely known, and was acknowledged in an interview with Guy on March 23, 1983, that acceptable bids were targeted to average about 10% below a hospital's previous average costs reimbursed by the Medi-Cal program. Thus, hospitals were expected to offer per diem rates based on their historical costs, rather than competing against other hospitals' prices. Nevertheless, there is no evidence that hospitals were told, or that they figured out, that a particular historically based price was expected of them. Because not all hospitals' bids were being accepted and because at least some hospitals that badly wanted contracts were turned down, there is every reason to believe that hospitals perceived themselves to be competing with each other—both in bid price and in services and terms offered. Hospitals throughout the state took this competition seriously after three hospitals in San Francisco that had provided inpatient care to 40% of that city's Medi-Cal recipients did not receive contracts. After filing legal challenges to their exclusion, these hospitals later were given contracts, but the effect of this early rejection had a significant impact on other hospitals in California.[3]

Negotiations were conducted individually with all hospitals in one or a few clustered Health Facilities Planning Areas (HFPAs), health planning units previously designated by the state and used by the Czar as the basic geographic contracting unit. Negotiations continued until the Czar achieved at least the targeted contracted bed capacity and negotiations were completed with all facilities especially sought by the Czar. The area was then "closed."

Negotiations began in Los Angeles County in November 1982 and lasted for seven months. Virtually all of the acute care general hospitals in Los Angeles County applied for contracts. By May 1983, contracting in 17 of the county's 19 HFPAs had been completed. Of the 136 hospitals in these closed areas, contracts were awarded to all 6 county hospitals (100%) and 78 private hospitals, the latter making up 60% of the 130 not-for-profit and investor-owned acute care general hospitals in the area.

Because the details of the contracts and of the decision-making process are still secret, the purpose of this article will be to deduce from the only information available to the public—that is, the names of hospitals with contracts and available data and characteristics of the hospitals themselves—how well the legislated criteria were implemented in awarding contracts. Because the criteria included issues of access and quality-related characteristics, this analysis will permit some assessment of the hospital services available to Medi-Cal recipients as a result of the contracts.

Methodology

Contracting and noncontracting hospitals were compared on the basis of qualitative and quantitative data that would provide a profile of a hospital's characteristics that reflect the legislative criteria and be readily available. For several legislative objectives—protection against fraud and abuse (criterion 5), presence of labor management collective bargaining contracts (9) and, of course, price—information was not available for analysis.

Data for all 136 short-term acute-care general hospitals in Los Angeles County that were eligible for contracting were obtained from the California Health Facilities Commission,[4] American Hospital Association,[5] Hospital Council of Southern California,[6] California Department of Health Services,[7] Office of the Special Negotiator,[8] the Health and Hospital Marketing Databank[9] and local Professional Standards Review Organization (PSRO) offices.* Other information pertaining to the negotiating process was obtained from interviews with current and former officials of the California Department of Health Services, the Office of the Special Negotiator and hospital administrators. Hospitals in the two HFPAs in Los Angeles County that had not yet been closed at the time of this study have been excluded from the analysis. Also excluded from the analysis were Children's Hospital of Los Angeles, psychiatric and drug rehabilitation hospitals and other specialty facilities that had been exempted from the contracting process.

Beneficiary Access

Two of the legislative criteria (1 and 6) specifically direct the Czar to consider access in negotiating contracts. In this analysis, three dimensions of access were considered: disruption of sources of inpatient care that some Medi-Cal recipients will experience because their usual hospitals did not receive contracts, a phenomenon generally termed "redirection"; availability of entry points into the inpatient system through hospital outpatient services, and availability of specialty inpatient services.

Redirection

Disruption of Medi-Cal recipients' patterns of care was measured by comparing the percentage of Medi-Cal patient-days in contract and noncontract hospitals before the contract system. It is widely assumed that preventing Medi-Cal recipients from using certain hospitals would, in itself, disrupt their patterns of care and constitute some temporary reduction in access. We examined the percentage of Medi-Cal patient-days in contract and noncontract hospitals reported to the California Health Facilities Commission (CHFC) during fiscal year 1980-1981. Of the more than one million Medi-Cal patient-days, 83.8% were provided in hospitals that subsequently received Medi-Cal contracts (Table 1).

*Dr Daniel Wilner of the Health and Hospital Marketing Databank assisted us.

Thus, some 16.2% of Medi-Cal patients in Los Angeles County had to change from their previous source of inpatient care to another hospital. The percentage of redirected patient-days in Los Angeles County is comparable with that of the state as a whole. Statewide, in areas closed by August 1983, 14% of Medi-Cal patient-days would be redirected. Although admissions or discharges would be a better measure of redirection, the CHFC reports only patient-days by a patient's source of payment. Because the data are used comparatively, patient-day provides a satisfactory, relative measure of redirection. (Statewide, 15% of discharges would be redirected, compared with 14% of patient-days.[10])

The percent of redirection varies considerably among HFPAs. The HFPAs range from no redirection in four HFPAs to 100% redirection in HFPA 937, which had a tiny Medi-Cal inpatient volume. In HFPAs with more than 10% redirection, one or two noncontract hospitals that previously had substantial Medi-Cal loads account for most of the redirection. For example, in HFPA 909, one noncontract hospital accounts for 93.3% of redirected patient-days; in HFPA 917, one hospital accounts for 84.2%, and in HFPA 927, one hospital accounts for 72.9%. In HFPA 915, three hospitals account for 83.1% of redirection. In several HFPAs, redirection is spread over several hospitals, most of which had very small shares of the Medi-Cal service volume in the HFPA.

Clearly, not granting contracts to hospitals with large shares of their HFPA's Medi-Cal volume constitutes a change in the source of inpatient care for a substantial number of persons. Although any disruption of patterns of care-seeking may be undesirable, redirecting inpatient care alone is probably the least disruptive because, compared with ambulatory care, it is infrequently used by most beneficiaries and because doctors, not patients, usually determine the hospital to which a patient is admitted. Hospital contracting applied to inpatient care only, not emergency room or outpatient department use—although a few hospitals, like Cedars-Sinai in Los Angeles, tried to redirect their Medi-Cal outpatients to contract hospitals when they did not get a contract. Except for cases such as Cedars-Sinai, the disruption is undoubtedly more problematic for admitting physicians than for their patients unless the contract hospitals are a considerable distance from a patient's home.

As is obvious from the percent of redirection resulting from the contracting outcomes, the contracting process favored hospitals that had provided greater shares of Medi-Cal inpatient days in their HFPA. County hospitals, of course, were the largest Medi-Cal providers in their areas, accounting for an average of 55.3% of the Medi-Cal inpatient days for their HFPAs. Among private hospitals, those that received contracts provided an average of 13.2% of their HFPA inpatient days compared with 7.9% for noncontract hospitals (data not shown in table form).

TABLE 1.—*Proportion of Medi-Cal Patient-Days Redirected From Noncontract Hospitals**

Area	Total Medi-Cal Patient-Days in Acute Care Hospitals, FY 1980-1981	Percent of Medi-Cal Patient-Days in Noncontract Hospitals, FY 1983-1984
Los Angeles County	1,003,425	16.2
HFPA 901	32,114	4.2
HFPA 903	22,299	2.2
HFPA 905	49,019	24.2
HFPA 907	21,841	0.0
HFPA 909	21,258	12.1
HFPA 911	21,116	9.8
HFPA 913	53,860	17.0
HFPA 915	31,257	80.6
HFPA 917	18,706	32.9
HFPA 919	20,083	0.0
HFPA 921	122,447	6.2
HFPA 923	35,757	0.0
HFPA 925	305,687	15.9
HFPA 927	62,946	42.1
HFPA 933	126,353	16.2
HFPA 935	57,782	0.0
HFPA 937	900	100.0

FY=fiscal year, HFPA=Health Facilities Planning Area

*From the Report to the Legislature on the Operations of the Office of Special Health Care Negotiations, Appendix K[8] and Individual Hospital Data for California, 1980-1981.[4]

Entry to Inpatient Care

For many Medi-Cal patients, emergency rooms are an entry point to hospital inpatient care as well as an important source of ambulatory care. Although finding emergency room physicians willing to admit and care for Medi-Cal patients has been a continuing problem in the Medi-Cal program, it is assumed that such patients have a better chance of being admitted when necessary if a hospital has at least a basic emergency room with a physician on duty than if it has only standby or first-aid referral services or no emergency license at all.

Of the hospitals that received contracts, 59.5% have at least basic emergency rooms (Table 2). All but two HFPAs include one or more contract hospitals with at least basic emergency services. Because Medi-Cal recipients may receive emergency inpatient and outpatient care from any licensed hospital, even in those HFPAs without basic emergency services under contract, Medi-Cal patients have

TABLE 2.—*Contract and Noncontract Hospitals by Particular Services Available**

Service	Contract Hospitals: County	Contract Hospitals: Private	Contract Hospitals: Total (%)	Noncontract Hospitals (%)	All Hospitals
At least basic emergency room	4/6†	46/78‡	50/84 (59.5)	33/51 (64.7)§	135
Obstetrical services	3/6†	47/78‡	50/84 (59.5)	22/52 (42.3)§	136
Neonatal intensive care unit	3/6†	13/78‡	16/78 (19.0)	3/52 (5.8)§	136

*From Annual Roster and Press Manual,[6] Health Facilities Directory,[7] Report to the Legislature on the Operations of the Office of the Special Health Care Negotiations, Appendix K[8] and 1984 Hospital Marketing Directory: Hospitals in Southern California.[9]

†County hospitals with service versus total county hospitals.

‡Private contract hospitals with service versus total private contract hospitals.

§Private noncontract hospitals with service versus total private noncontract hospitals.

TABLE 3.—*Contract and Noncontract Hospitals by Peer Group**

Type of Hospital	Contract Hospitals			Noncontract Hospitals (%)	All Hospitals (%)
	County (%)	Private (%)	Total (%)		
Teaching or large complex	3 (9.1)	20 (60.6)	23 (69.7)	10 (30.3)	33 (100.0)
Moderately complex	†	22 (56.4)	22 (56.4)	17 (43.6)	39 (100.0)
Smaller urban and rural	†	29 (61.7)	29 (61.7)	18 (38.3)	47 (100.0)
Other	3 (17.6)	7 (41.2)	10 (58.8)	7 (41.2)	17 (100.0)

*From Individual Hospital Data for California, 1980-1981[4] and Report to the Legislature on the Operations of the Office of Special Health Care Negotiations, Appendix K.[8]

†No Los Angeles County Department of Health Services hospital of this type.

the same access to emergency services as other insured population groups. But in one HFPA with more than 31,000 general acute care inpatient days reported in 1980-1981, Medi-Cal recipients may experience less access to inpatient care under the contract arrangements because none of the contract hospitals has a basic emergency room. Despite the generally adequate distribution of contract hospitals with emergency rooms, hospitals without even basic emergency rooms were slightly more likely to receive contracts than hospitals with them.

Specialty Inpatient Services

In addition to the criteria that specifically mentioned access, the legislature also mandated the Czar to consider a hospital's "ability to provide or arrange needed specialized services" (criterion 4), an access-related concern. Once appointed, the Czar indicated that certain services of special importance to Medi-Cal patients would be considered in the contracting process. Obstetrical care is important to the Medi-Cal population because, with the elimination of medically indigent adults from Medi-Cal and the continued ability of elderly Medi-Cal patients with Medicare to obtain inpatient care from any licensed hospital, a large proportion of Medi-Cal beneficiaries affected by selective contracting are recipients of Aid to Families With Dependent Children (AFDC) and AFDC-related medically needy persons.

Of all contract hospitals, 59.5% have obstetrical units (Table 2). Only one small HFPA is without obstetrical services in contract hospitals. The Czar estimates that the availability of such services is adequate for the Medi-Cal population's needs, but it is difficult to determine from the data whether or not they are sufficiently accessible. With these services and with emergency care, travel times to such hospitals must be taken into account as well as availability of obstetricians who accept Medi-Cal (an issue beyond the control of the Czar) to adequately evaluate access.

Of the 72 hospitals in Los Angeles County with obstetrical services, 69.4% received contracts. Thus, it appears that the contracting favored hospitals with obstetrical services and that the accessibility of these services to Medi-Cal beneficiaries is at least minimally protected.

Similarly, access to neonatal intensive care is important to Medi-Cal recipients, a disproportionately high percentage of whom are likely to have high-risk pregnancies and low-birthweight or distressed infants. Of all contract hospitals, 19.0% have a neonatal intensive care unit (NICU), compared with only 5.8% of noncontract hospitals (Table 2). Because relatively few hospitals have an NICU, there are five HFPAs without any contract or noncontract hospital that provides neonatal intensive care services. One additional HFPA includes a noncontract private hospital that provides an NICU. This pattern indicates that the Czar generally contracted with at least one hospital with an NICU in each HFPA when such hospitals were available.

Technical Complexity

The reform legislation instructed the Czar to consider a hospital's ability to provide tertiary care needed on a regional basis (criterion 7) and, in effect, include within a given area adequate provisions for more severe or complex medical problems (criterion 8). A hospital's ability to provide a complex level of care could be measured by the range or quantity of services it provides. An alternative method available in California is simply to compare hospitals on the basis of their classification by the CHFC into peer groups based on size, scope of service, service volumes and other factors.

Of the four peer group combinations considered in this study, teaching and large complex hospitals were more likely to receive contracts than the other three types (Table 3). Seven of every ten such tertiary care hospitals received contracts compared with about six of every ten among all technically less complex facilities. These more complex hospitals tended to be high-volume Medi-Cal providers so there was a strong incentive for the Czar to include them within the Medi-Cal contract system.

Four HFPAs are without any teaching or large complex hospital, either contract or noncontract. Three of these HFPAs are fairly rural areas with relatively low population density. One, however, is an urban area with a large low-income population. Though there was no tertiary care hospital in the HFPA with which the Czar could have contracted, it is a fairly narrow HFPA and Medi-Cal recipients may have adequate access to tertiary care hospitals in neighboring HFPAs. In addition to these four HFPAs that have no large technically sophisticated hospitals, another HFPA has a teaching or large complex hospital not under contract; this is a surburban area with several low-income communities, apparently none of which is near a tertiary care hospital under contract to the Medi-Cal program.

Quality of Care and Utilization Controls

The legislature directed the Czar to consider a hospital's "ability to render quality services" (criterion 3) and also specifically mentioned quality in criterion 6. In addition, Guy expressed a desire to include as many "name" hospitals as possible; these are generally large, prestigious hospitals with a broad scope of services and widely recognized as providing good quality medical care. They are also likely to have teaching programs. Quality of care is difficult to measure. It

would also have been difficult to develop a list of "name" hospitals because a survey of physicians or patients in the county was not feasible for this study.

We used two measures that are quality-*related*—delegated PSRO status and teaching status. A hospital with a utilization review mechanism approved by the Professional Standards Review Organization may be considered both as a recognized method of controlling utilization (criterion 2) and as a measure of quality, assuming the utilization review identifies and corrects grossly inappropriate medical practices. Hospitals that do not have approved internal review procedures and committees must submit to external review by the area PSRO. The value of PSRO delegation as a measure of quality is limited in part by variations in the ease with which different regional PSROs delegate responsibility to hospitals.

Utilization review has been developed mainly to control excessive utilization. This was a problem for third-party payers because fee-for-service and cost-based reimbursement systems create incentives for physicians and hospitals to do more procedures and services than may actually be needed. The new Medi-Cal per diem method of reimbursing hospitals reverses that incentive for hospitals (though not for physicians), providing incentives to do less for patients because hospitals receive the same daily rate regardless of how many services are used. Utilization review committees may concern themselves with such issues, although existing computerized monitoring systems in the Medi-Cal program cannot identify patterns of "underutilization" because they were designed for "overutilization." In any case, PSRO delegation remains a useful, albeit imperfect, measure for judging quality assurance.

Delegated PSRO status is closely associated with teaching status, which is taken as an additional quality-related factor. (Teaching status and PSRO delegation are not completely independent variables. Among the 127 hospitals for which information about both variables was available, 90.9% of the teaching hospitals have PSRO delegation compared with 56.2% of the nonteaching hospitals.) Hospitals with even modest teaching programs are more likely to attract physicians with a higher degree of technical proficiency than hospitals with no teaching component. Of course, the technical influence of teaching programs may be limited to the services included in the program, but in any given area we assumed that having a teaching program would give the hospital a favorable reputation within the medical community.

Hospitals with PSRO delegation were only slightly more likely to receive contracts than those without it. Of the 79 hospitals in Los Angeles County with delegation, 64.6% received contracts, compared with 60.4% of the 53 hospitals without delegation (Table 4). The contracting process thus resulted in a slightly higher percentage of contract hospitals having PSRO delegation (61.4%) than noncontract hospitals (57.1%).

Contract hospitals are far more likely than noncontract hospitals to have teaching programs. Of the 22 hospitals in the county with American Medical Association-approved residency programs, 20 (90.9%) received Medi-Cal contracts (Table 5). Because of the small number of teaching hospitals, they still constitute only 24.4% of all contract hospitals.

Operating Efficiency

The legislature directed the Czar to consider a hospital's ability to provide services "efficiently and economically" (criterion 3). For this study, contract and noncontract hospitals were compared on the basis of two measures of efficiency: occupancy rates, because it was assumed that hospitals with fewer empty beds would be able to spread all their fixed costs and some of their variable costs across more revenue-producing patients, and the ratio of full-time equivalent (FTE) employees to average daily census (ADC) of patients, because hospitals with lower FTE/ADC ratios use less staff per patient. To adjust for the occupancy and staffing differences related to hospital size and complexity of care, contract and noncontract hospitals were analyzed within peer groups. FTE/ADC ratios were available for only 107 of the hospitals in this study. Smaller urban and rural hospitals and "other hospitals" are especially plagued by lack of information on this variable, introducing potentially substantial errors in the findings for these peer groups and possibly the "all hospitals" figures. The more complex hospital peer groups should not be much affected.

The mean occupancy rate for contract hospitals was 55.6% compared with 49.5% for noncontract hospitals

TABLE 4.—*Contract and Noncontract Hospitals by PSRO Delegation**

PSRO Delegation	Contract Hospitals			Noncontract Hospitals (%)	All Hospitals (%)
	County	Private	Total (%)		
Delegated	6	45	51 (64.6)	28 (35.4)	79 (100.0)
Nondelegated	0	32	32 (60.4)	21 (39.6)	53 (100.0)

PSRO=Professional Standards Review Organization

*From Report to the Legislature on the Operations of the Office of Special Health Care Negotiations, Appendix K.[8] PSRO delegated-status information was obtained by personal communication from each regional PSRO office.

TABLE 5.—*Contract and Noncontract Hospitals by Teaching Programs**

Teaching Programs	Contract Hospitals			Noncontract Hospitals (%)	All Hospitals (%)
	County	Private	Total (%)		
Has program	5	15	20 (90.9)	2 (9.1)	22 (100.0)
No program	1	61	62 (57.4)	46 (42.6)	108 (100.0)

*From Guide to the Health Care Field[5] and Report to the Legislature on the Operations of the Office of Special Health Care Negotiations, Appendix K.[8]

(Table 6). Both contract and noncontract hospitals that were more complex tended to have higher occupancy rates than less complex facilities. Only among the most complex peer group did noncontract hospitals have higher occupancy on the average than contract hospitals.

Contract hospitals tend to have larger ratios of FTE employees to average daily census (Table 7). These differences remain even within three of the four peer group categories, with hospitals offering more complex care having higher FTE/ADC ratios as expected. Interestingly, moderately complex hospitals have higher mean FTE/ADC ratios than teaching and large complex hospitals. (When only private hospitals are compared, contract and noncontract teaching and large complex hospitals have essentially the same ratios, 4.9 and 4.8, respectively, suggesting that often the sicker and more difficult-to-manage cases in the county hospitals require more staffing.)

Although contract hospitals have slightly higher occupancy rates, they also may have higher FTE/ADC ratios. The occupancy rates are probably not sufficiently higher among the contract hospitals to affect their average costs per patient-day, but their FTE/ADC ratios do suggest greater expense per patient-day for this variable cost factor. Without access to the bid or final contract prices, it is impossible to know whether these differences were reflected in higher per diem bids. However, these data do suggest that if efficiency was taken into account by the Czar, other factors weighed more heavily in the award of contracts.

Commitment to the Poor

In addition to examining the Czar's fulfillment of legislated criteria, other issues aroused concern among many observers. One concern, expressed by us and other analysts, was the prospect that hospitals with a demonstrated commitment to serving the poor might not receive contracts whereas hospitals that had no such commitments might underbid to keep their options open in a time of uncertainty. The argument in support of this hypothesis was that hospitals that were heavily dependent on Medi-Cal revenues would have to bid their average costs because Medi-Cal patients made up such a large share of their total patient-days, and that hospitals with a low volume of Medi-Cal service could bid their marginal costs (which would be lower than average costs) because Medi-Cal charges were a relatively insignificant part of their revenue. The fear was that hospitals that had shown a commitment to serving the poor but that did not receive contracts might become so financially distressed that they would be forced to close, depriving the poor and the community of socially useful institutions. Guy did not alleviate this concern when he announced early in the negotiating process that he would treat every hospital as a competitor in an economic market and not as a social institution that must be preserved.

A hospital's commitment to serving the poor was measured by several factors: the percentage of its inpatient and outpatient revenues derived from serving Medi-Cal patients; the ratio of outpatient visits to inpatient days, because low-income persons are more dependent on clinics and hospitals for ambulatory care than are the more affluent and adequately insured population, and whether the hospital reported an operating deficit in fiscal year 1980-1981. Operating deficits are associated with providing uncompensated care to uninsured and poor patients and with serving a greater proportion of Medi-Cal recipients because Medi-Cal paid a lower percentage of all costs than did other third-party payers. In 1979, Blue Cross and commercial insurance companies reimbursed hospitals 12% more than their "full financial requirements" (including the actual costs of providing care plus working capital and capital replacement costs), Medicare reimbursed them 4% less than their full costs and Medi-Cal paid them 18% less than their full costs, according to a study by the CHFC.[11]

County hospitals, as expected, have the greatest commitment to serving the poor as shown by their great dependence on Medi-Cal inpatient and outpatient revenues (Table 8). Similarly, they have a high average ratio of outpatient visits to inpatient days. All six county hospitals reported an operating deficit in 1980-1981, as they do every year.

Private hospitals that received contracts were substantially more dependent on Medi-Cal for their inpatient revenues than noncontract hospitals, and they were slightly more dependent on Medi-Cal for their outpatient revenues as well, although they had slightly lower ratios of outpatient visits to inpatient days. More than a third of all private contract hospitals reported operating deficits in 1980-1981 compared with only a fourth of their noncontract counterparts.

TABLE 6.—*Occupancy Rate of Contract and Noncontract Hospitals by Peer Group**

Peer Group	Contract Hospitals (%)	Noncontract Hospitals (%)
All hospitals	84 (55.6)	52 (49.5)
Teaching and large complex hospitals	23 (64.9)	10 (68.7)
Moderately complex hospitals	22 (55.4)	17 (53.4)
Smaller urban and rural hospitals	29 (50.2)	18 (43.0)
Other hospitals	10 (50.0)	7 (29.2)

*From individual Hospital Data for California, 1980-1981[4] and Report to the Legislature on the Operations of the Office of Special Health Care Negotiations, Appendix K.[8]

TABLE 7.—*FTE/ADC Ratio of Contract and Noncontract Hospitals by Peer Group**

Peer Group	Contract Hospitals (%)	Noncontract Hospitals (%)
All hospitals	70 (5.6)	37 (4.9)
Teaching and large complex hospitals	22 (5.3)	10 (4.8)
Moderately complex hospitals	20 (6.5)	16 (5.1)
Smaller urban and rural hospitals	20 (5.2)	10 (4.6)
Other hospitals	8 (5.1)	1 (7.1)

FTE/ADC=full-time equivalent [employees] to average daily census.

*From individual Hospital Data for California, 1980-1981,[4] Guide to the Health Care Field[5] and Report to the Legislature on the Operations of the Office of Special Health Care Negotiations, Appendix K.[8]

Discussion and Conclusion

The analysis of the outcome of the hospital contracting process in Los Angeles County suggests that the criteria established by the legislature were substantially achieved. First, access by Medi-Cal beneficiaries to inpatient hospital care seems to be reasonably well protected by selective contracting. A small percentage (16.2%) of Medi-Cal patient days must be redirected from noncontract hospitals to facilities with contracts, though the percentage of redirection within HFPAs varies considerably. Access to emergency

TABLE 8.—*Commitment to Serve the Poor by Contract and Noncontract Hospitals and Ownership**

Commitment to Serve the Poor	Contract Hospitals		Noncontract Hospitals	Number
	County	Private		
Mean percent inpatient revenue from Medi-Cal (%) . . .	37.9	13.4	8.3	128
Mean percent outpatient revenue from Medi-Cal (%) . .	11.0	3.3	3.0	136
Mean ratio of outpatient visits per inpatient day (%) . .	2.0	0.9	1.3	128
Percent hospitals with operating deficit reported in 1980-1981 (%)	100.0	35.9	26.9	136

*From Individual Hospital Data for California, 1980-1981,[4] and Report to the Legislature on the Operations of the Office of Special Health Care Negotiations, Appendix K.[8]

room services through which Medi-Cal recipients might be admitted to hospital for nonemergency problems seems generally adequate, although two HFPAs are without any contract hospital that has at least a basic emergency room. Only one HFPA has no obstetric inpatient services under contract. Access to neonatal intensive care services is more restricted because relatively few hospitals have such services. Two HFPAs seem deficient in the availability of technically sophisticated inpatient care, though one of the HFPAs is a rural area that is not far from other areas with contract hospitals.

Second, technically more sophisticated hospitals, especially those with teaching programs, were more likely to receive contracts. Whether these are truly higher quality hospitals is difficult to judge although our indicators—having a teaching program and PSRO delegation to an in-hospital utilization review committee—suggest that contract hospitals are, at the very least, not inferior.

Third, contract hospitals tend to have higher occupancy rates (except among teaching and large complex hospitals), but they also have higher ratios of full-time staff to average daily census. Although the Czar may have taken these or other measures of efficiency into account, other factors obviously carried more weight in the contracting process.

Fourth, hospitals with a demonstrated commitment to serving the poor tended to be more successful in winning contracts. In addition to the county hospitals, private hospitals that were more dependent on Medi-Cal inpatient revenues were more likely to receive contracts than hospitals that derived smaller percentages of their revenue from Medi-Cal. Similarly, hospitals that had reported operating deficits in fiscal year 1980-1981 were also more likely to receive contracts.

The contracting process seems to have worked well in Los Angeles County. The legislature's criteria were substantially met, Medi-Cal beneficiaries had access to inpatient care in general and to specialized and technically complex services in facilities of at least average quality. In general, hospitals with a demonstrated commitment to serving the poor are well represented among contract hospitals. It seems clear that the Czar considered hospital characteristics in a manner consistent with the legislature's criteria.

Some caution is warranted in concluding that Medi-Cal selective contracting is an unqualified success. First, this study has some methodologic limitations. The analysis has been made without measures of performance for several legislated criteria—protection against fraud and abuse, presence of labor-management collective bargaining contracts and price—and has used very imperfect measures of another criterion—quality. In addition, the analysis is based on hospitals only in Los Angeles County; the results of the contracting process may be somewhat different in other counties.

Second, this analysis focuses only on the outcome of the negotiating process—which hospitals got contracts and which did not—and characteristics of the Medi-Cal inpatient hospital system in place at the conclusion of the contracting process. We do not yet have any evidence concerning the long-term effect of contracting on either Medi-Cal recipients or on hospitals. It may work as it has been optimistically envisioned. Medi-Cal patients may not suffer any significant loss of access. Medi-Cal hospitals may make up in increased volumes for the (on average) lower patient-day revenues they now receive from Medi-Cal and simply eliminate unnecessary services they formerly provided to patients. On the other hand, contracting may develop into the more pessimistic scenario that many have predicted. Medi-Cal recipients' actual access to health care may be restricted considerably more than this analysis suggests. Contract hospitals with a heavy Medi-Cal load may receive substantially less revenue than their costs, have greater difficulties obtaining capital and end up providing second-class care to Medi-Cal recipients or closing their doors altogether.[2,3]

Our findings support the conclusion that the special negotiator substantially implemented the criteria for Medi-Cal selective contracting with hospitals established by the legislature, as represented by the outcome of contract negotiations in Los Angeles. It is too early, however, to judge the actual immediate or long-term consequences of the program on beneficiaries or hospitals.

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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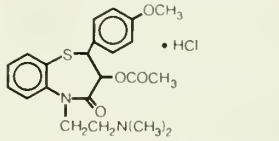
DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LOH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LO_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC DD88-1772-49). Each yellow tablet is engraved with MARIDN on one side and 1772 on the other.

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(Continued from Page 35)

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Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

OB/GYN

October 17-19—**9th Annual Pacific NW Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion/Jantzen Beach. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

September 6-7—**Ashland Conference: Infectious Disease.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 4-5—**Fifth Annual Toxicology Conference.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

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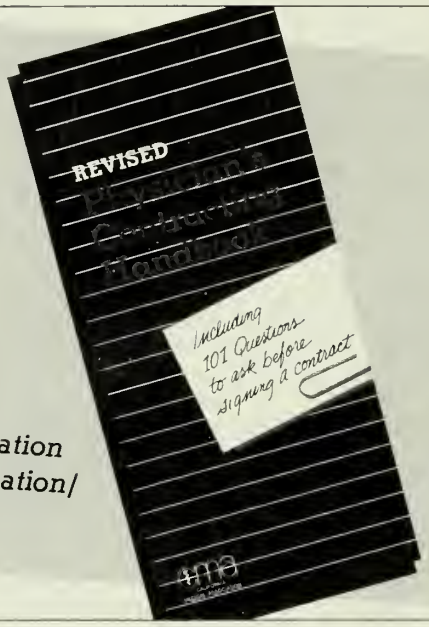

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HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

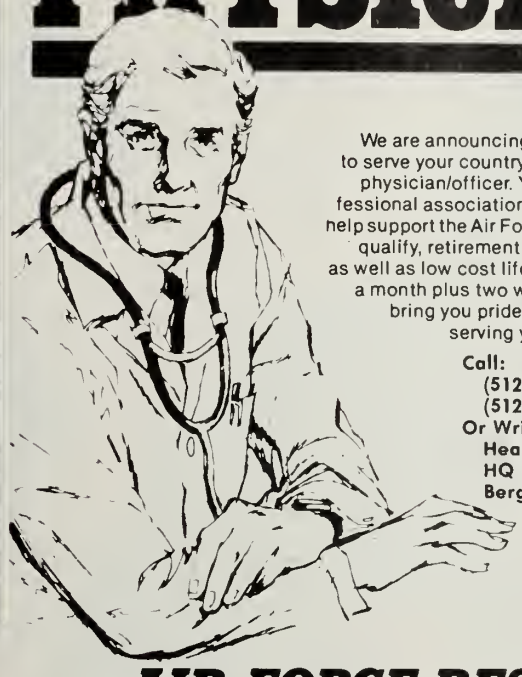
August 5-7—**Seminars in Ultrasound, CT, MR** (Sponsor: University of Utah). Monday-Wednesday. Hyannis, Massachusetts. 13.5 hrs. Contact: William Zwiebel, MD, (801) 581-2800.

August 22-25—**Intermountain Dermatology Society** (Sponsor: University of Utah). Thursday-Sunday. Red Fish Lake Lodge, Idaho. 9.5 hrs. Contact: C. David Hansen, MD, (801) 321-1100.

September 26-27—**Utah State Medical Association Annual Meeting.** Thursday-Friday. Hotel Utah, Salt Lake City. Contact: USMA, 540 E. Fifth South, Salt Lake City 84102. (801) 355-7477.

November 8-9—**Advanced Trauma Life Support** (Sponsor: University of Utah/Utah Department of Health). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Kim Tanner, (801) 533-6608.

PHYSICIANS



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WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111.(206) 223-6898.

August 2-4—**Washington State Society of Anesthesiologists Seafair VII Meeting—Anesthesia Care for Trauma.** Seattle. Friday-Sunday. Seattle Sheraton Hotel. Contact: U/W.

August 2-5—**Refractive Surgery—State of the Art.** Orcas Island. Friday-Monday. Rosario Resort. Contact: Patti Smith, Washington State Academy of Ophthalmology, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

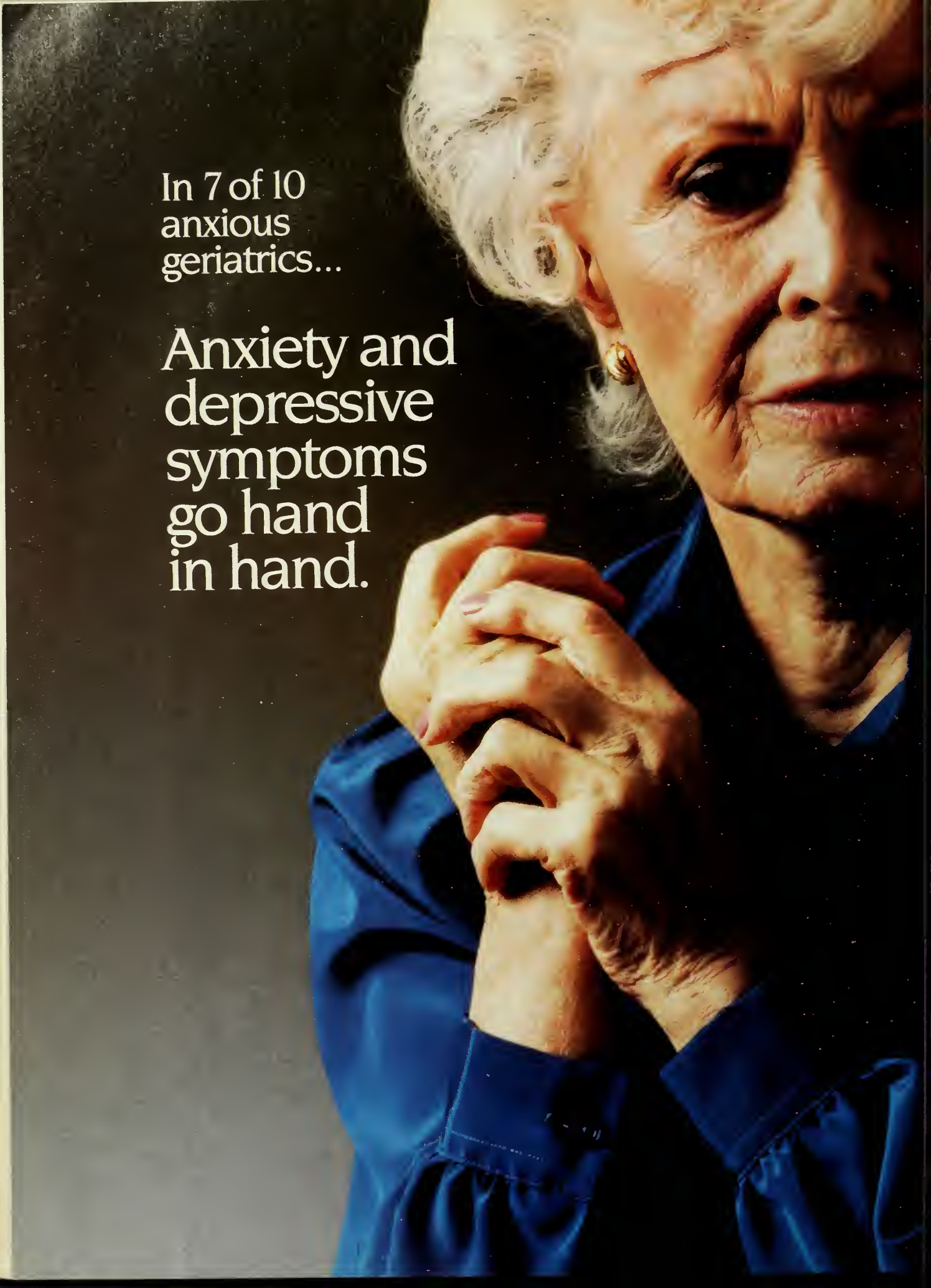
August 26-30 (OREGON)—**Psychiatry for Primary Care Physicians.** Monday-Friday. Sunriver Resort. Contact: U/W.

September 5-6—**Microbiology Update.** Seattle. Thursday-Friday. U/W Health Sciences. Contact: U/W.

September 6-7—**Washington State Society of Anesthesiologists Fall Meeting.** Hood Canal. Friday-Saturday. Alderbrook Inn. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

September 9-13—**Advances in Family Practice/ACLS.** Seattle. Monday-Friday. U/W Health Sciences. Contact: U/W.

(Continued on Page 132)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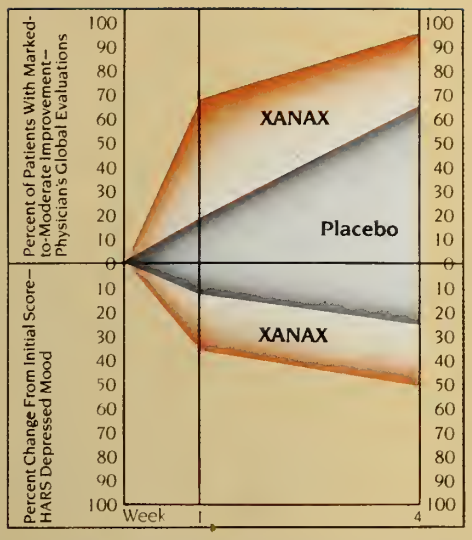

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1 Cohn JB Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984 35(1):100-112

Xanax® 0.25 mg Tablets
alprazolam IV

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Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions.* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility* No carcinogenic potential or impairment of fertility in rats *Pregnancy* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity *Labor and Delivery* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse *Pediatric Use* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular Tachycardia/palpitations, and hypotension

Sensory Blurred vision.

Musculoskeletal: Rigidity and tremor

Cutaneous. Dermatitis/allergy

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class.* XANAX is a controlled substance and has been assigned to schedule IV

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg. t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION B-3-S

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Kalamazoo, Michigan 49001 USA

CONTINUING MEDICAL EDUCATION

(Continued from Page 129)

September 19-22—**Washington State Medical Association Annual Meeting.** Jantzen Beach. Thursday-Sunday. Thunderbird Motor Inn. Contact: Patti Smith, WSMA, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

September 28-October 4 (SAN JUAN ISLANDS)—**Effective Management of Common Sports Injuries.** Saturday-Friday. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (206) 788-4995.

October 10-11—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. Westin. Contact: U/W.

October 24-25—**Alzheimer's.** Seattle. Thursday-Friday. Westin. Contact: U/W.

November 1-2 (VANCOUVER)—**Northwest Urological Society 1985 Annual Meeting.** Vancouver, BC. Friday-Saturday. Bayshore Inn. Contact: Patti Smith, Northwest Urological Society, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

November 7-8—**Washington Chapter, American College of Emergency Physicians—15th Annual Clinic Conference.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington Chapter, ACEP, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

December 7-8—**Washington State Society of Anesthesiologists Winter Meeting.** Seattle. Saturday-Sunday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

WYOMING

August 26-28—**Tutorials in the Tetons: Clinical Cardiology, Diagnostic and Therapeutic Advances.** Jackson Lake Lodge, Grand Teton National Park, Moran. Monday-Wednesday. Sponsor: American College of Cardiology. Contact: ACC, Extramural Prog. Dept., 9111 Old Georgetown Rd., Bethesda, MD 20814. (301) 897-5400, ext. 230.

September 7-12—**Applications in Preventive Medicine.** Yellowstone National Park Bicycle Tour. Saturday-Friday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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WYOMING—ER STAFF POSITION—Emergency Room in Rawlins, WY with moderate volume. Independent contractor status. Malpractice paid. Very flexible schedule. Excellent hunting, fishing, backpacking and skiing in surrounding area. Send Résumé to: Duane Eugene Abels, DO PC, PO Box 1536, Rawlings, WY 82301 or call (307) 324-2221 x115.

FAMILY PRACTICE PHYSICIAN to join 15 physician multispecialty group located in Southern Idaho. Send résumé to Business Administrator, Box 1233, Twin Falls, ID 83301.

INSTITUTION PHYSICIAN needed to staff the Wyoming State Training School at Lander, Wyoming. We have 420 mentally retarded residents with a 30 bed Health Care Center with a staff of four physicians. Attractive salary and fringe benefits. No overhead. Pleasant surrounding area including an excellent medical group in Lander. If interested, please contact the Personnel Manager, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520. An Equal Opportunity Employer.

FAMILY PRACTICE opportunity in eastern New Mexico. Join two physicians in private practice situation with an established patient population. Must do OB. No buy-in; just share expenses and call. Family community with stable economy. Contact Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext. 3050.

EUGENE, OREGON: FP/GP to join staff in salaried position with clinic providing outpatient and hospital care primarily to low income population. Half-time to start, flexible scheduling. Contact: Michael Weinstein, MD, 323 East 12th Ave, Eugene, OR 97401; (503) 484-4800.

ACADEMIC GENERAL INTERNISTS, CARDIOLOGIST, AND ENDOCRINOLOGIST, DO—Wanted for full-time faculty positions. Must be Board admissible or certified, interested in teaching medical students and house staff. Good balance between clinical practice and teaching with research opportunities available. Assistant Professor level with excellent guaranteed salary and benefits. Send CV to Victor H. Kaylarian, DO, Department of Medicine, University of Osteopathic Medicine and Health Sciences, 3200 Grand Ave., Des Moines, IA 50312. All inquiries confidential.

KETCHUM, SUN VALLEY, IDAHO: Internist, Surgeon, Pediatrician, Orthopedist in multispecialty, expanding, well-equipped clinic. Income moderate; quality of life highest. Dr Bryan Stone, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

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OCCUPATIONAL MEDICINE STAFF POSITION available in well known Gulf South Multispecialty Clinic. Established full service occupational medicine program undergoing expansion. Excellent support from outstanding medical staff. Possible university appointment. Must be Board eligible/certified in Occupational Medicine with formal training in Occupational or Preventative Medicine. Excellent fringe benefits, salary negotiable. Send reply and CV to Box 6478, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

GENERAL SURGEON OR FAMILY PRACTITIONER with general survery credentials wanted for a rural Washington State community. Full service hospital with drawing area of 6,000. Office space and ancillary services offered. Good opportunity in an agricultural four-season recreational area. Contact: Garvin Olson, Administrator, Janice Davis, Secretary, 1012 South Third, Dayton, WA 99328; (509) 382-2531.

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All of these advantages mean **security** for the Westworld physician. If your commitment is to the highest standards in patient care, and if a rural environment sounds inviting to you, investigate Westworld Community Healthcare. We have a variety of attractive practice opportunities in rural America. Call collect now for more information, or send your curriculum vitae to: **Mr. Joel Feinstein, Dept. PH-3, (714) 768-2981, Westworld Community Healthcare, Inc., 83832 Rockfield Rd., Lake Forest, CA 92630-2880.** We are an equal opportunity employer m/f.

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CALIFORNIA—Join a partnership of established physicians providing urgent and ambulatory care in both northern and southern California. Physicians earn a guaranteed minimum with a strong incentive package and have the opportunity to quickly become partners. Our attractive centers are rapidly growing! Please indicate your geographic preference (Los Angeles or San Francisco Bay Area) and contact: California Emergency Physicians, 440 Grand Ave., Suite 500, Oakland, CA 94610; (415) 832-6400.

(Continued on Page 136)

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(Continued from Page 133)

PHYSICIANS WANTED

PHYSICIAN WANTED: San Francisco B/C or B/E Internist/FP to join growing three man primary care group in San Francisco's Mission District. For further information contact Dr John Pierce, (415) 826-7575 or send résumé to Golden Gate Medical Group, 3620 Army St., San Francisco, CA 94110.

INFECTIOUS DISEASE AND INTERNAL MEDICINE—The Division of General Internal Medicine/Primary Care at Cook County Hospital wishes to recruit an Attending Physician to supervise care of both patients with general medical problems and patients with AIDS. Board eligibility in Internal Medicine is required; subspecialty training in Infectious Disease or Oncology is desirable. General Medicine responsibilities occupy 50 percent time and include ward attending and supervising the General Medicine Clinic. AIDS service responsibilities include participation in biweekly clinics and regular ward consultations for patients with AIDS and AIDS related conditions, and involvement in educational and research programs of the AIDS service. Sensitivity to the health care needs of gay men and other AIDS risk group members is needed. Starting salary for Board certified physicians is $54,228 a year. For further information please contact Renslow Sherer, MD, Coordinator of AIDS Services, Division of General Medicine, Cook County Hospital, 1835 W. Harrison, Chicago, IL 60612. Cook County Hospital is an Equal Opportunity/Affirmative Action Employer.

INTERNIST-RHEUMATOLOGIST-SUBSPECIALIST. Opportunity to join solo Internist-Rheumatologist in private practice. Assocation and investment opportunity. Laboratory and x-ray. Send CV to R. S. Gordon, MD, 5945 Brockton Ave., Riverside, CA 92506.

WASHINGTON—Ambulatory Care Center, Tacoma. Full- or possibly part-time for FP/IM/EM trained physician. Contact Roger Simms, MD, (206) 759-6655 or reply with CV to 5702 North 26th, Tacoma, WA 98407.

HEMATOLOGIST-ONCOLOGIST to join Oncologist in progressive multispecialty group practice located in suburban San Francisco area. University affiliation and NCOG protocol participation encouraged. Competitive salary and benefits leading to partnership. Send résumé to Box 6479, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTICE-INTERNAL MEDICINE-SURGEON. Multispecialty clinic in Northern Idaho Panhandle. Nominal lease includes fully-equipped office and treatment suites with receptionist and janitorial services provided. Clinic includes lab, x-ray and pharmacy. Billing services available. Located in a four-season playground rich with forests, lakes, streams and wild game. Just 20 minutes from a 14-run ski resort. Attractive lifestyle. For information: (208) 784-1221, ext. 304. Mail résumé to: Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

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PHYSICIANS WANTED

FAMILY PRACTITIONER—OUTPATIENT CARE: Full time position available for residency trained, Board Eligible/Board Certified Family Practitioner interested in a position involving outpatient care. Pediatrics, Prenatal Care, Adult Medicine, Orthopedics, and minor surgery responsibilities are available. For information, call Donald B. Dawson, Director of Physician Staffing, toll-free at 1 (800) 446-2255 [in California call 1 (800) 336-2255]. FHP Professional Staffing, 400 Oceangate Blvd., Suite 1317, Long Beach, CA 90802. For opportunities in Utah, call Maryalys Poulson collect at (801) 355-1234.

FAMILY PRACTITIONER—Full time position available for residency trained, Board Eligible/Board Certified Family Practitioners interested in practicing in a comprehensive care environment. Outpatient care and in-hospital responsibilities are offered in a growing family practice organization. Administrative opportunities also available. For information, call Donald B. Dawson, Director of Physician Staffing, toll-free at 1 (800) 446-2255 [in California call 1 (800) 336-2255]. FHP Professional Staffing, 400 Oceangate Blvd., Suite 1317, Long Beach, CA 90802. For opportunities in Utah, call Maryalys Poulson collect at (801) 355-1234.

CALIFORNIA, SAN JOSE: Emergency Physician sought for position as part-time Director of Poison Control Center at a university-affiliated teaching hospital. Responsibilities include patient care in the Emergency Department. Must be Board Prepared/Board Certified in Clinical Toxicology. Fee-for-service with minimum guarantee. Contact: James B. Lane, MD, 1625 The Alameda, #201, San Jose, CA 95126; (408) 293-8881.

CALIFORNIA—Board Certified/eligible or residency trained emergency physician wanted to join 320 physician multispecialty group. Competitive salary and excellent fringe benefits. Ninety miles from Sierra skiing and San Francisco. California license required. Send curriculum vitae to Mrs. Carolyn Whelan, The Permanente Medical Group, Inc., PO Box 254999, Sacramento, CA 95825. An equal opportunity employer.

GENERAL INTERNIST—BC/BE to join four man group of internists located in beautiful central coastal community. Senior partner retiring January 1986. Excellent opportunity for young energetic physician; salary plus percentage if mutually satisfactory. Write: Box 6482, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PATHOLOGIST: Large pathology group seeking qualified anatomic and clinical pathologist. Excellent position with growth potential. Send résumé to: Glenview Pathology Medical Group, 9331 Venice Blvd., Culver City, CA 90230.

PHYSICIANS WANTED

TIBURON, CALIFORNIA: Senior Internist seeking Internist or other specialist willing to share small, well-equipped and well-staffed office, one to three days each week. For terms and particulars call Mrs. Grossi, (415) 435-0656. Business hours 9:30-5:00.

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(Continued on Page 138)

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(Continued from Page 136)

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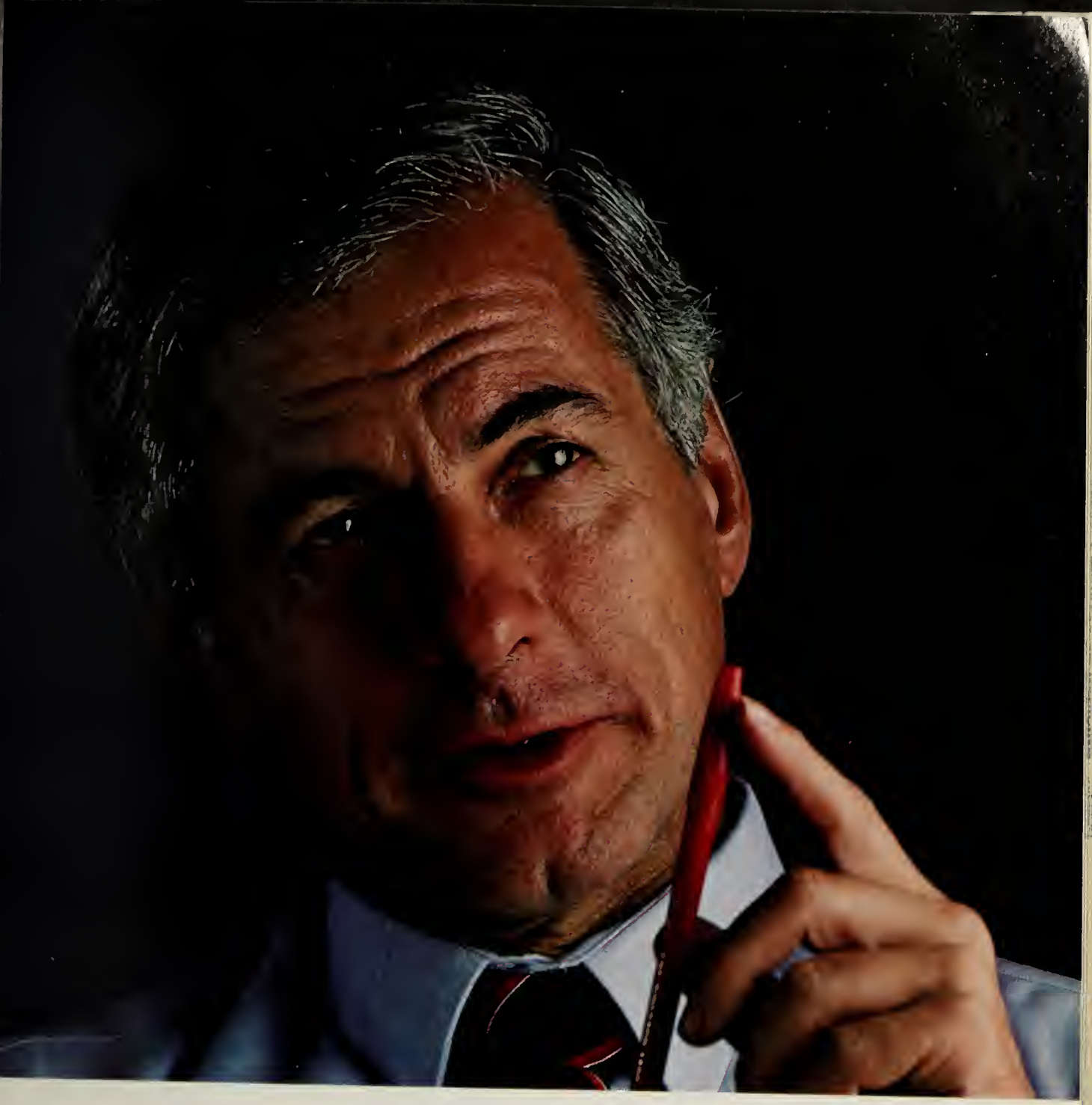

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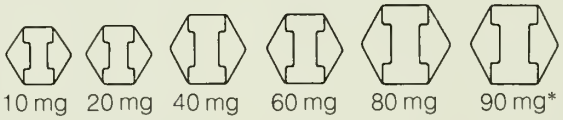

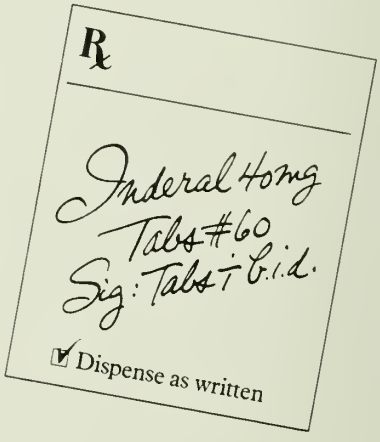

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INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General. Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: 1986: date and place to be announced.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1986: date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1986: date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1986: date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1986: date and place to be announced.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets*, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets*, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

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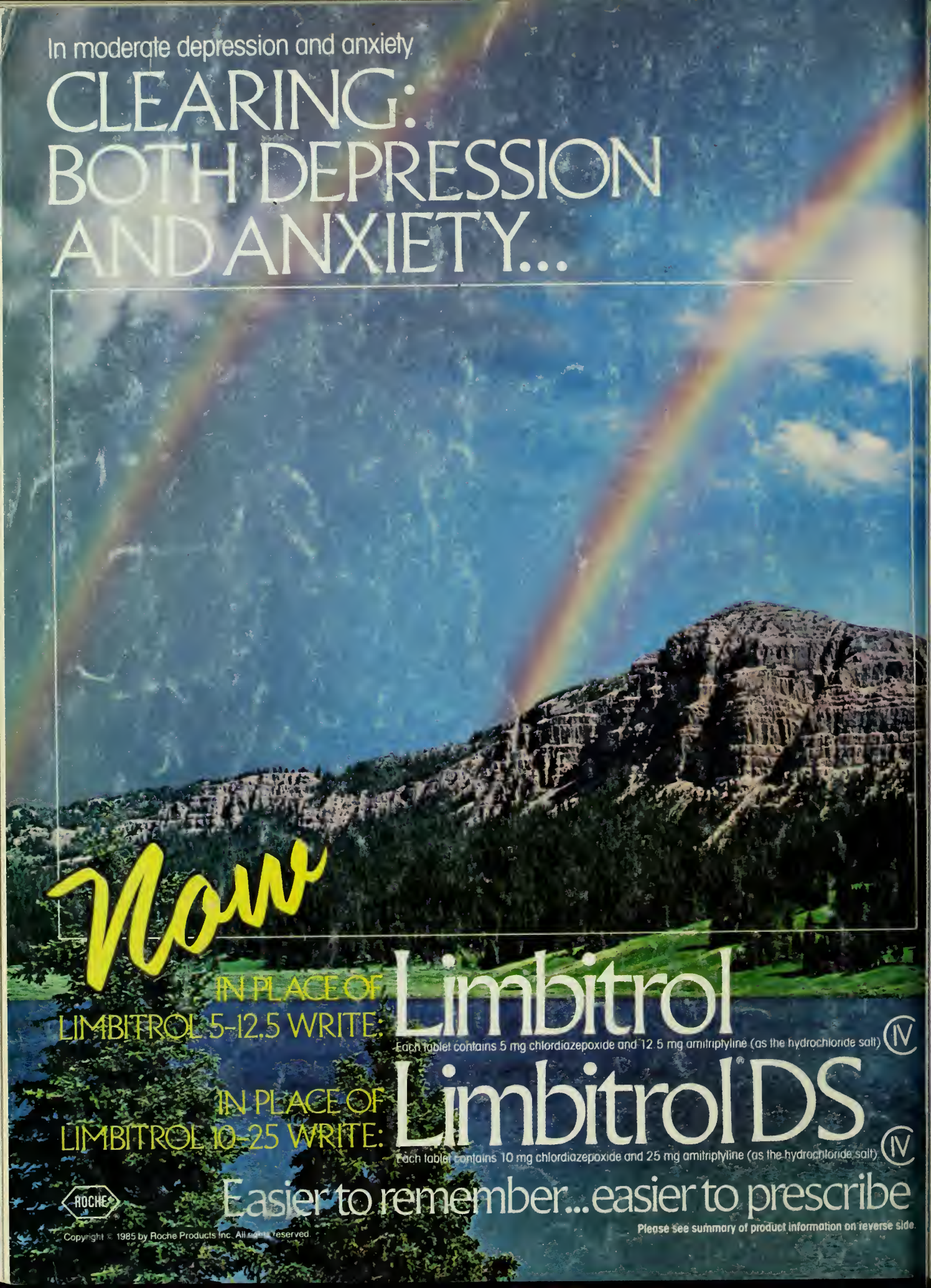

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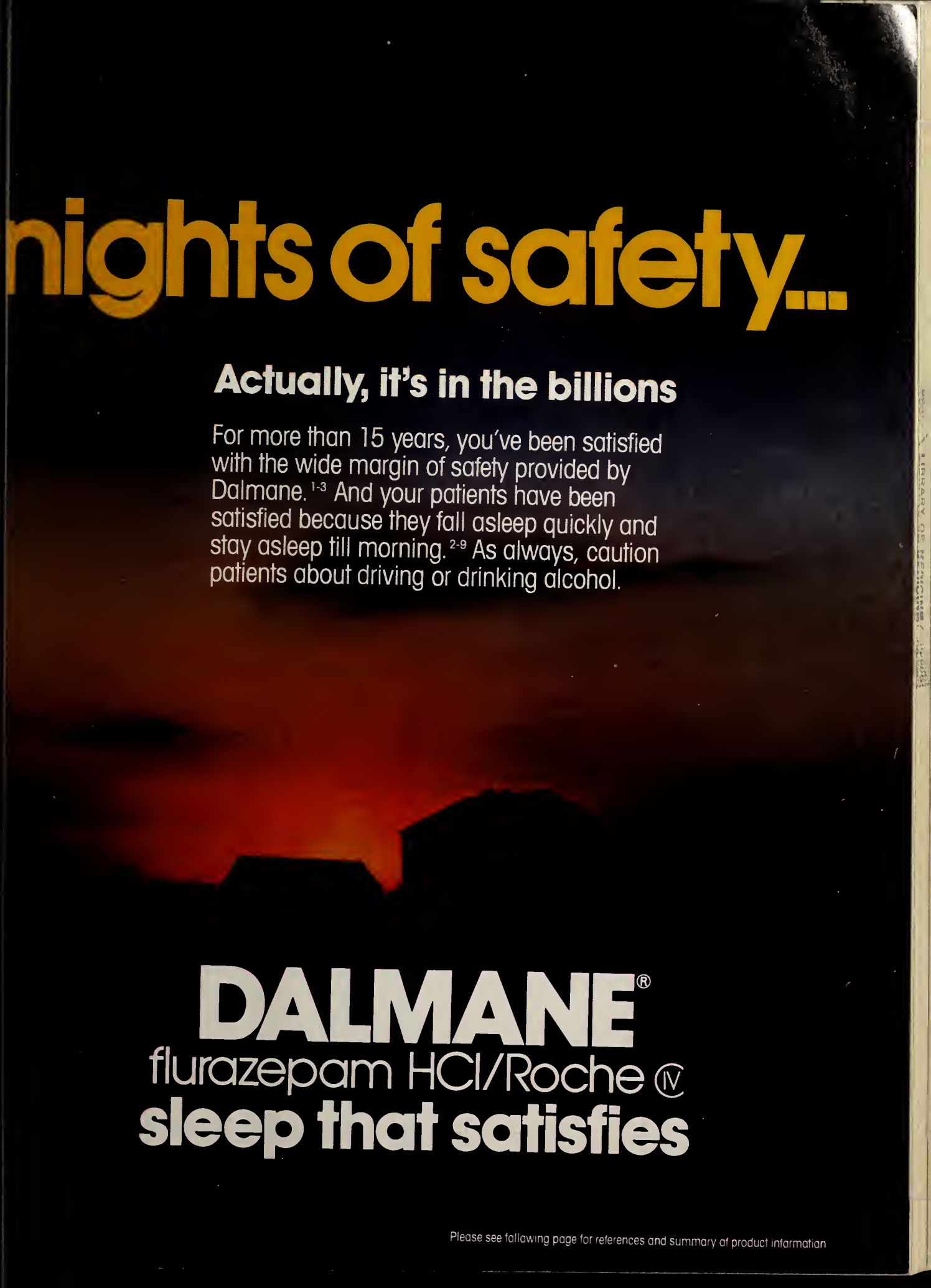
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Incidence Less Than 1%—Probable Causal Relationship*
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence Less Than 1%—Causal Relationship Unknown*
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis, cataracts; **Hematologic:** Bleeding episodes (eg, epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction, acidosis; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema; **Renal:** Renal papillary necrosis.

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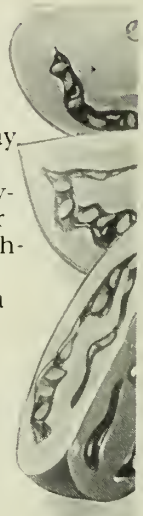

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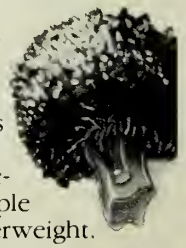
Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.

A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12-year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.

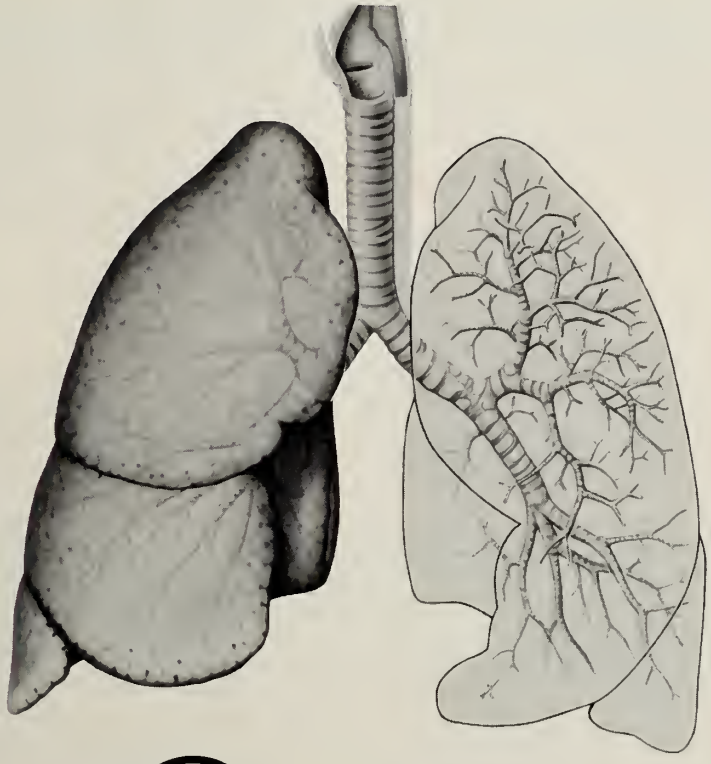


Now, more than ever, we know you can cook up your own defense against cancer. So eat healthy and be healthy.

No one faces cancer alone.

AMERICAN CANCER SOCIETY®

Consider the causative organisms...



Ceclor®
cefaclor
250-mg Pulvules® t.i.d.

offers effectiveness against the major causes of bacterial bronchitis

H. influenzae, *H. influenzae*, *S. pneumoniae*, *S. pyogenes*
(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[D617B2R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Additional information available to the profession on request from Eli Lilly and Company Indianapolis, Indiana 46285

Eli Lilly Industries, Inc
Carolina, Puerto Rico 00630

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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When the pain and inflammation of arthritis flare up...

- FELDENE is an excellent choice for osteoarthritis and rheumatoid arthritis. Beginning with the first dose, FELDENE provides effective and long-lasting relief of arthritis pain and stiffness.[1]
- Convenient once-daily dosage provides round-the-clock relief of symptoms[2]—encouraging compliance and enhancing productivity at home and on the job.[3]

Start one-a-day

Feldene® (PIROXICAM) 20 mg capsules

For full anti-arthritic action

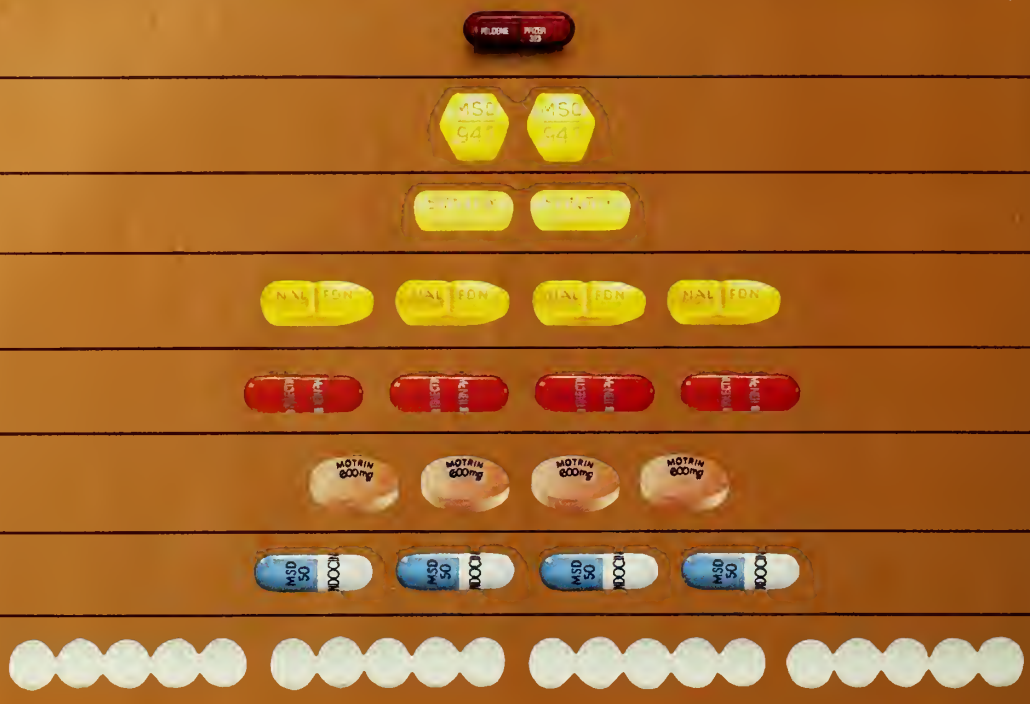
Please see a brief summary of FELDENE (piroxicam) prescribing information on the following page.

Start one-a-day

Feldene® (PIROXICAM) 20 mg capsules

For full anti-arthritic action

Prescribe one 20mg capsule daily for convenience and compliance



Source: PDR, 1985; Manufacturers' Prescribing Information.

Indicates maximum dosage for osteoarthritis and rheumatoid arthritis for the antiarthritic agents included. Consult manufacturers' prescribing information.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice and dogs.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with FELDENE. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress*, nausea*, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenital: BUN and creatinine elevations (see PRECAUTIONS)

Body as a Whole: headache, malaise

Special Senses: tinnitus

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

*Reactions occurring in 3% to 9% of patients treated with FELDENE (piroxicam).

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Special Senses: swollen eyes, blurred vision, eye irritations

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis

Dermatologic: onycholysis, loss of hair

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias

Urogenital System: dysuria

Body as a Whole: weakness

Cardiovascular/Respiratory: palpitations, dyspnea

Hypersensitivity: positive ANA

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis. It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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References: 1. Siegmeth W: Serum concentrations of piroxicam in relation to its clinical effect in patients with chronic polyarthritis. *Wien Med Wochenschr* (special issue):31-35, 1980. 2. Tausch G: Placebo-controlled study of piroxicam in the treatment of rheumatoid arthritis. *Am J Med* (report) 72:18-22, February 1982. 3. Fogari R: Quality of life as a measure of therapeutic response. *Int Med* (special suppl):37-43, 1984.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

USING COMPUTERS IN THE PRACTICE OF MEDICINE—Professional and Clinical Guidelines for Managing Your Practice and Improving Patient Care—Morton Solomon, MD. Prentice-Hall, Inc, Englewood Cliffs, NJ 07632, 1985. 344 pages (softbound), no price given.

VIOLENCE IN THE MEDICAL CARE SETTING—A Survival Guide—Edited by James T. Turner, PhD, Clinical Psychologist, VA Medical Center, and Department of Psychiatry, University of Tennessee Center for Health Sciences, Memphis. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1984. 271 pages, $31.50.

WORK & HEALTH—IT'S YOUR LIFE—Phillip L. Polakoff, MD, MPH, Assistant Clinical Professor, Stanford University School of Medicine, Stanford, California, and University of California, Irvine, School of Medicine. Press Associates, Inc, 806 15th St NW, Suite 632, Washington, DC 20005, 1984. 231 pages, $7.95 (paperback).

YAG LASER BRONCHOSCOPY—Volume Five in Surgical Sciences Series—J. F. Dumon, MD, ECCP; in collaboration with S. Shapshay, MD; B. Meric, MD; L. Garbe, MD; P. Fuentes, MD; R. Pons, MD, and M. Kasbarian, MD, Endoscopy Unit, Salvator Hospital, Marseilles, France, Praeger Publishers, 521 Fifth Avenue, New York, NY 10175, 1985. 122 pages, $23.

MNEMONICS, RHETORIC AND POETICS FOR MEDICS—Volume II—Robert L. Bloomfield, MD, and Carolyn F. Pedly, MD, Department of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC. Harbinger Press, PO Box 17201, Winston-Salem, NC 27116, 1984. 165 pages (softbound), no price given.

THE PARENT'S PEDIATRIC COMPANION—Gilbert Simon, MD, General Pediatrics Practitioner, Sacramento, California, and Marcia Cohen. William Morrow & Company, 105 Madison Ave, New York, NY 10016, 1985. 378 pages, $17.95.

PHYSICIAN'S HANDBOOK—Twenty-First Edition—Marcus A. Krupp, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine, and Director of Research, Palo Alto Medical Research Foundation, Palo Alto, California; Lawrence M. Tierney, Jr, MD, Associate Professor of Medicine, University of California, San Francisco, School of Medicine, and Assistant Chief, Medical Service, VA Medical Center, San Francisco; Ernest Jawetz, MD, PhD, Professor of Microbiology and Medicine Emeritus, and Robert L. Roe, MD, Associate Clinical Professor of Medicine, University of California, San Francisco, and Carlos A. Camargo, MD, Associate Professor of Clinical Medicine, Stanford University School of Medicine, and Director of Endocrine Clinic, Stanford University Hospital, Stanford, California. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1985. 800 pages, $16.50.

READINGS IN MEDICAL ARTIFICIAL INTELLIGENCE—The First Decade—Edited by William J. Clancey, PhD, Department of Computer Science, Stanford University, and Edward H. Shortliffe, PhD, MD, Assistant Professor of Medicine and Computer Science, Stanford University School of Medicine, Stanford, California. Addison-Wesley Publishing Company, 2727 Sand Hill Road, Meno Park, CA 94035, 1984. 512 pages, $39.95.

REMODELING YOUR PROFESSIONAL OFFICE—Murray Schwartz, DDS. Medical Economics Books, Oradell, NJ 07649, 1985. 202 pages, $26.95*, plus $2 handling. *Note: Price is subject to change without notice.

SIGNS AND SYMPTOMS IN NEUROLOGY—Edited by Phillip D. Swanson, MD, PhD, Professor of Medicine and Head, Division of Neurology, University of Washington School of Medicine, Seattle. J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105, 1984. 401 pages, $29.50.

STROKE: FROM CRISIS TO VICTORY—A Family Guide—John H. Lavin. Franklin Watts, 387 Park Avenue South, New York, NY 10016, 1985. 182 pages, $15.95.

TAX STRATEGY—Third Edition—Lawrence Farber, Senior Editor of *Medical Economics*. Medical Economics Books, Oradell, NJ 07649, 1985. 248 pages, $25.95.

TEXTBOOK OF PAIN—Edited by Patrick D. Wall, DM, FRCP, Director, Cerebral Functions Research Group, and Professor, Department of Anatomy, University College, London, and Ronald Melzack, PhD, Professor, Department of Psychology, McGill University, Montreal. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 840 pages, $105.

TROPICAL UROLOGY AND RENAL DISEASE—Edited by I. Husain, MB, FRCS, Senior Urological Consultant, Central and Mafraq Hospital, Abu Dhabi, United Arab Emirates, and Lately Assistant Professor of Urology, College of Medicine, King Saud University, Riyadh, Saudi Arabia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 435 pages, $55.

VIRAL HEPATITIS AND LIVER DISEASE—Edited by Girish N. Vyas, PhD, Professor of Laboratory Medicine and Chief of Transfusion Service, University of California, San Francisco, School of Medicine; Jules L. Dienstag, MD, Associate Professor of Medicine, Harvard Medical School, and Assistant Physician, Gastrointestinal Unit, Massachusetts General Hospital, Boston, and Jay H. Hoofnagle, MD, Senior Investigator, Liver Diseases Section, Digestive Diseases Branch, National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland. Grune & Stratton, Inc, Orlando, FL 32887, 1984. 711 pages, $69.95.

WHAT'S NEW IN ALLERGY—Stephen Astor, MD. Two A's Industries, Inc, 285 South Drive, Mountain View, CA 94040, 1985. 181 pages, $8.50 (paperback), Quantity rates are available.

SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed:

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg, for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg)

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Wilmington, DE 19897

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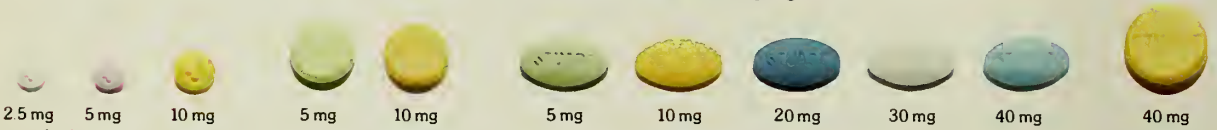

2.5 mg 5 mg 10 mg
Sublingual Tablets

5 mg 10 mg
Chewable Tablets

5 mg 10 mg 20 mg 30 mg 40 mg
Oral "Swallow" Tablets

40 mg
Sustained Action "Swallow" Tablets

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CAPOTEN® (captopril tablets) is almost never associated with fatigue (unlike beta-blockers and CNS active agents: e.g., clonidine, methyldopa).‡[1]

CAPOTEN is almost never associate with loss of libido and impotence (unlike beta-blockers and CNS active agents).‡[1,2]

†CAPOTEN is indicated for the treatment of hypertensive patients who on multidrug regimens either have failed to respond satisfactorily or have developed unacceptable side effects.
Please see the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the brief summary on adjacent pages.

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CAPOTEN® BID
captopril tablets

HYPERTENSION CONTROL† PATIENTS CAN FEEL GOOD ABOUT

CAPOTEN is almost never associated with mental impairment (unlike beta-blockers and CNS active agents).‡[3]

ACE*INHIBITOR
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HELP PUT QUALITY BACK INTO LIVING

iotensin Converting Enzyme

most frequently occurring adverse reactions associated with
OTEN are skin rash and taste alteration; both effects are generally
l, reversible, or self-limited.

ACE INHIBITOR

CAPOTEN® BID
captopril tablets

Precautionary guidelines

CAPOTEN® (captopril tablets) has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the immune response. The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

References:

1 The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. US Department of Health and Human Services, June 1984

2. Stevenson JG, Umstead GS: Sexual dysfunction due to antihypertensive agents. Drug Intell Clin Pharm 18:113-121, 1984

3 Solomon S, Hotchkiss E, Saravay SM, et al: Impairment of memory function by antihypertensive medication. Arch Gen Psychiatry 40:1109-1112, 1983.

*Angiotensin Converting Enzyme

†Please see brief summary for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

CAPOTEN* TABLETS
Captopril Tablets

INDICATIONS: Hypertension – Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria – Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about one-fourth of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all of the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the eighth month of therapy. Patients should have urinary protein estimates (dip-stick on first morning urine, or quantitative 24-hour urine – the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approximate monthly intervals for the first nine months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis – Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about two weeks (other than two patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the first 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the first 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first two weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the first 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity – In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(continued on next page)

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Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril-treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the first 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.
Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658B)

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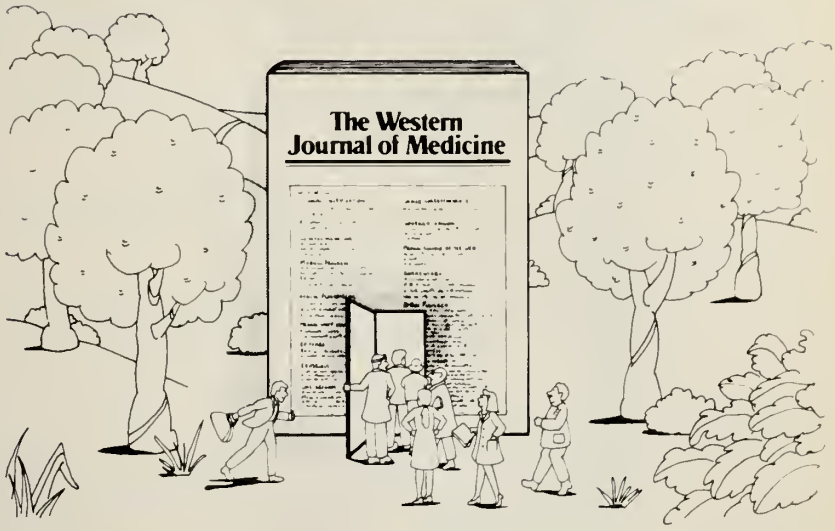

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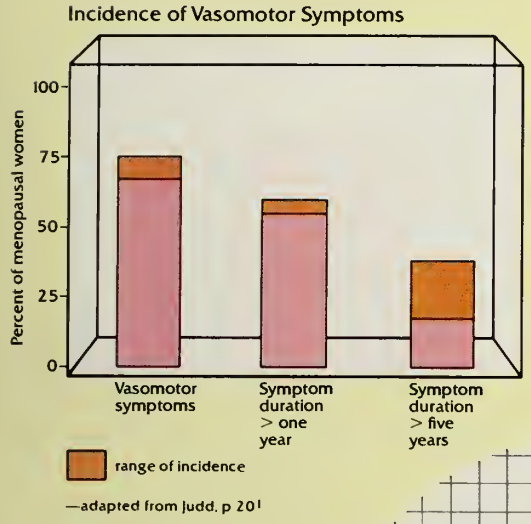
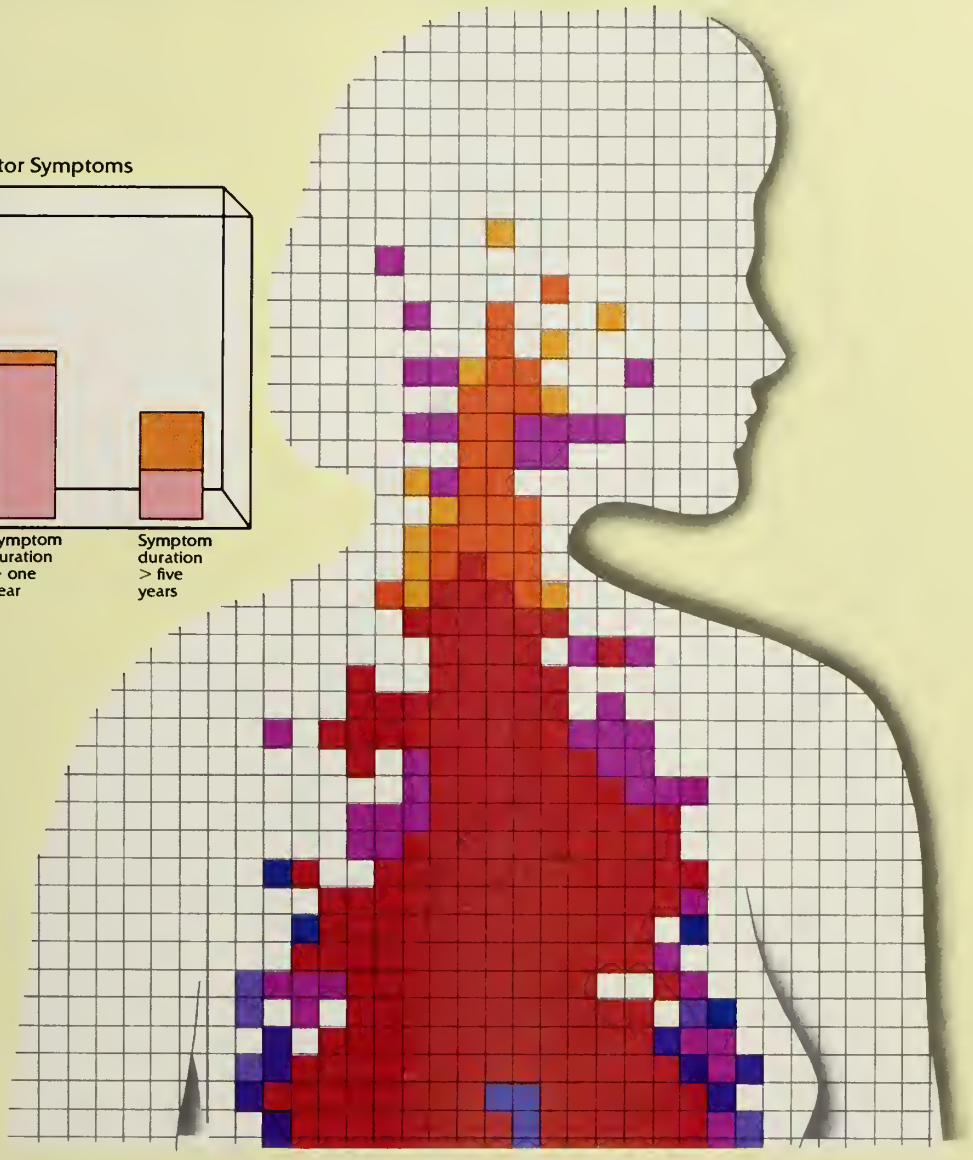
VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION



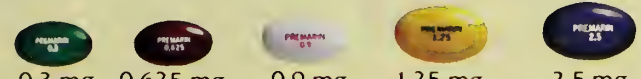


PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years.[1] These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[2]—the treatment of choice for moderate to severe vasomotor symptoms.[3] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

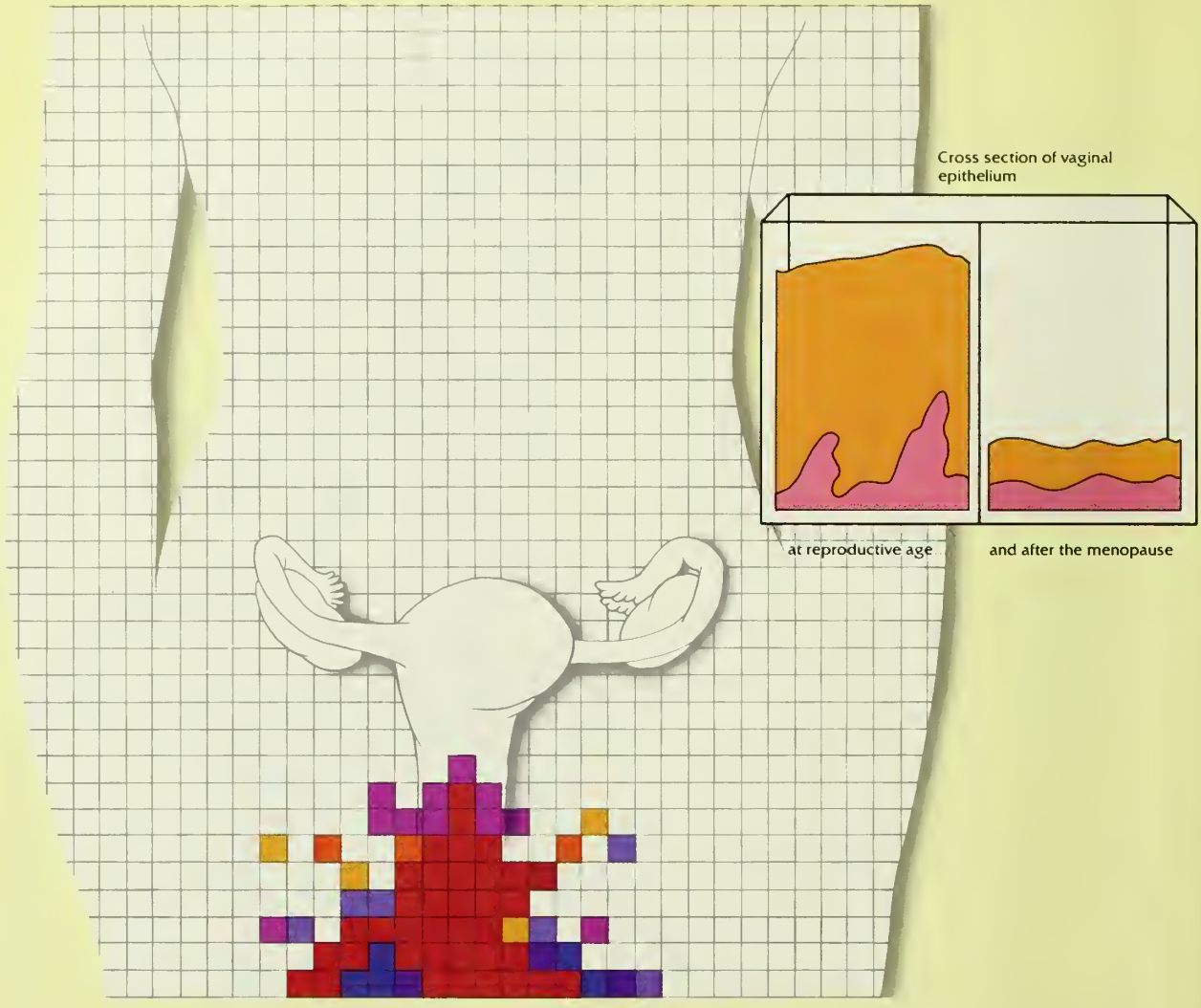


0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

Please see last page for brief summary of full prescribing information.

VAGINAL ATROPHY THAT INTERFERES WITH SEXUALITY



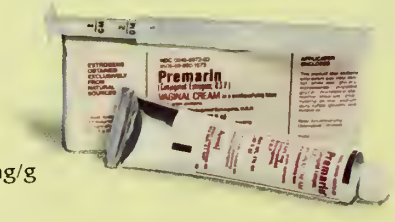
PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

PREMARIN®

(CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream



0.625 mg/g

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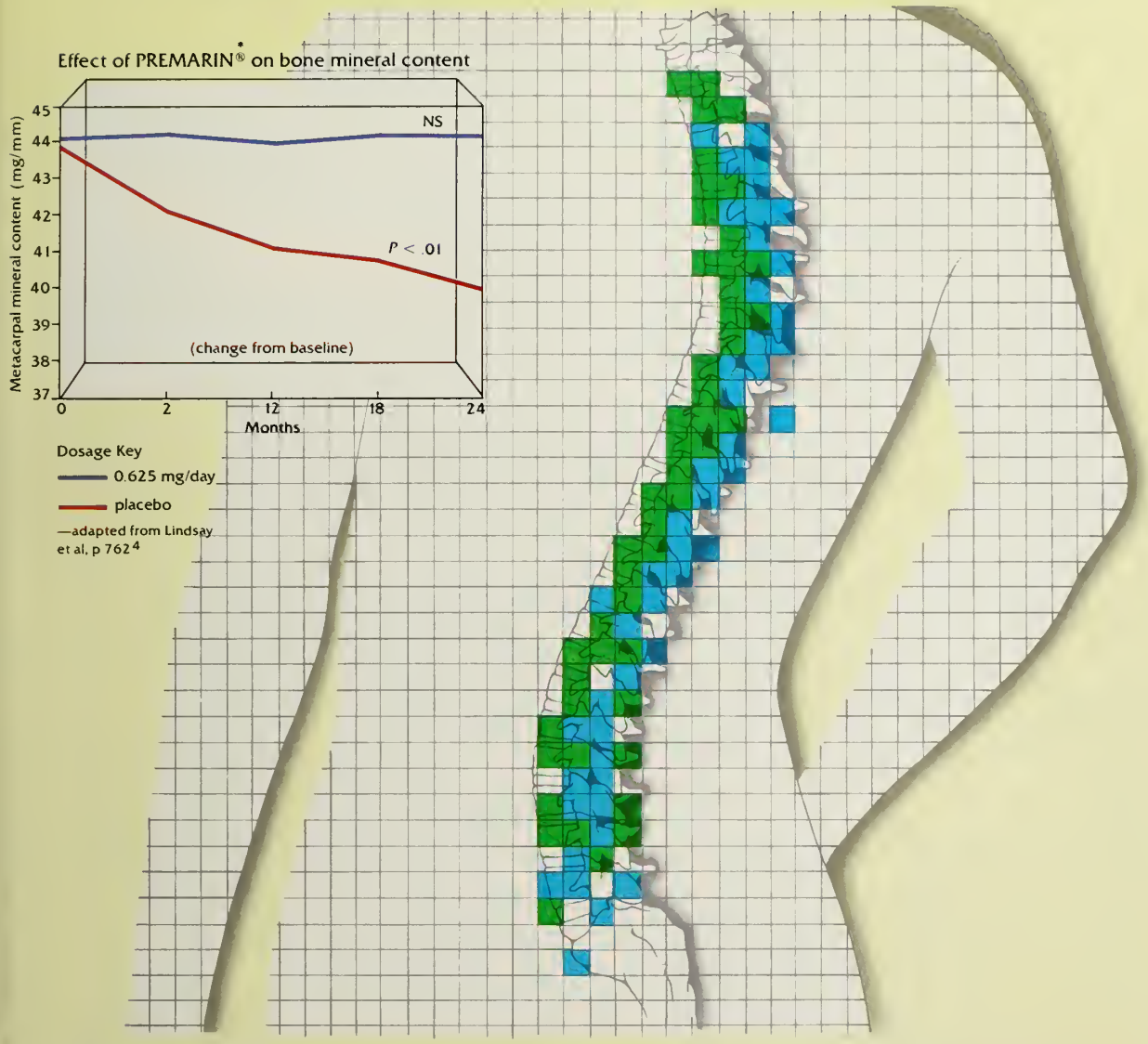
Please see last page for brief summary of full prescribing information.

POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES

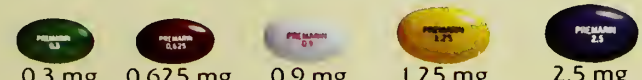


PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.[5] The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.[6]

To minimize osteoporotic damage, the condition must be detected early and treated promptly. For many patients, PREMARIN is optimal therapy for osteoporosis, as part of a comprehensive program that includes exercise, good nutrition, and calcium supplements. In a controlled study of postmenopausal and oophorectomized women, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) doses of 0.625 mg/day prevented loss of metacarpal mineral content (see graph above).[4]

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued, erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria, edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only: For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. B65—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. B66—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. B68—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. B72—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **4340R2/785**

REFERENCES: 1. Judd HL: After the menopause. *Transition* 1983;1:19-30. 2. Erlik Y, Tataryn IV, Meldrum OR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 3. Meldrum OR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983;1(February):11-17. 4. Lindsay R, Hart OM, Clark OM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984;63:759-763. 5. Katz WA: *Rheumatic Diseases: Diagnosis and Management*. Philadelphia, JB Lippincott Co, 1977, p 672. 6. Reese WO: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983;22(November):116-131.

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From the Division of General Internal Medicine and the Institute for Health Policy Studies, the Division of Bioethics, University of California, San Francisco, School of Medicine.

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Dr Livingston is in private practice in family medicine, with special interest in back problems, in Richmond, British Columbia.

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Ms McCaw is a fourth-year medical student in the Joint Medical Program, University of California, San Francisco, School of Medicine, and University of California, Berkeley, and Dr DeLay is Assistant Clinical Professor, Departments of Family Practice and of Epidemiology and International Health, University of California, San Francisco, School of Medicine, and Director, Refugee Medical Clinic, San Francisco General Hospital Medical Center.

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ABBA I. TERR, MD; ALEX WEISSKOPF, MD, and ROBERT A. SPARACINO
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★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

ANNOUNCING SOME NEW FINDINGS ON CHOLESTEROL.

Perhaps rather surprisingly, beef has no more cholesterol than chicken. Even roast chicken without skin.

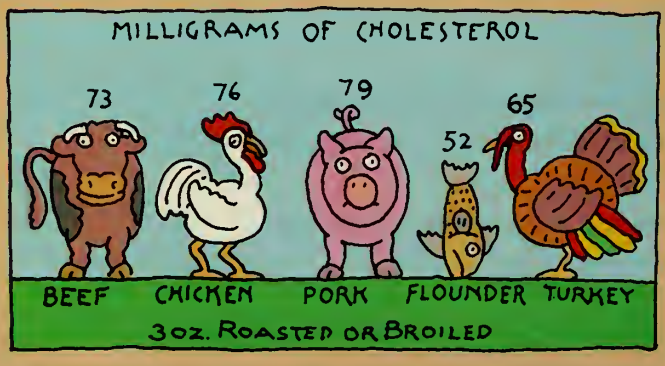
That was the finding of a new U.S.D.A. study on beef nutrient composition.*

That same study found beef is lower in calories than ever.

And lower in fat.

In fact, three ounces of beef now has just 192 calories and a modest nine grams of fat, over half of which is unsaturated.

Today, new breeding and feeding techniques are making beef a whole different animal. Though not so different that it isn't still one of the body's bes sources of iron, zinc, B-vitamins and protein.



It all means moderate portions of beef can fit easily int a reduced cholesterol, low saturated fat diet.

And that can stop a lot of squawking when you recommend one.

For more information on the new U.S.D.A. study and beef's contribution to healthy eating in the eighties, write to Beef Nutrition, California Beef Council, 551 Foster City Boulevard, Suite A, Foster City, California 94404.

*Beef data from 1983 Beef Nutritive Composition Studies conducted by the U.S.D.A. and National Live Stock and Meat Board.

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Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • MONTANA • NEW MEXICO • OREGON • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

September 13 —**Advances in Fetal Echocardiography '85.** St. Joseph's Hospital and Medical Center, Phoenix. Friday. Contact: CME and Outreach Department, St. Joseph's Hospital and Medical Center, (602) 285-3000.

September 21—**Gastroenterology.** Phoenix. Saturday. Contact: U of A.

October 12—**Practical Approach to Fluid and Electrolytes.** Tucson. Saturday. Contact: U of A.

October 18-19—**Geriatric Medicine.** Boswell Memorial Hospital, Sun City. Friday-Saturday. Contact: Western Division, American Geriatrics Society, (602) 977-1877.

October 25-26—**Therapeutic Advances: New Choices for Medical Management of Disease.** Poco Diablo Resort, Sedona. Friday-Saturday. Contact: U of A.

November 1-2—**5th Annual Southwestern Poison Symposium.** Friday-Saturday. Contact: U of A.

November 9—**Cardiology.** Phoenix. Saturday. Contact: U of A.

November 15-16—**Arizona Chapter, American College of Surgeons.** Loews Ventana Canyon Resort, Tucson. Friday-Saturday. Contact: U of A.

November 25-27—**Cemented Versus Uncemented Revision Total Joint Arthroplasty.** Registry Resort, Scottsdale. Monday-Wednesday. Contact: Medical Meetings Department, St. Luke's Medical Center, (602) 251-8402.

December 7—**Psychiatry.** Tucson. Saturday. Contact: U of A.

CONTACT INFORMATION

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 95724. (602) 626-6173.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

August 16-18—**Summer Conference on Allergy, Rheumatology and Orthopedic Surgery.** Scripps

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KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

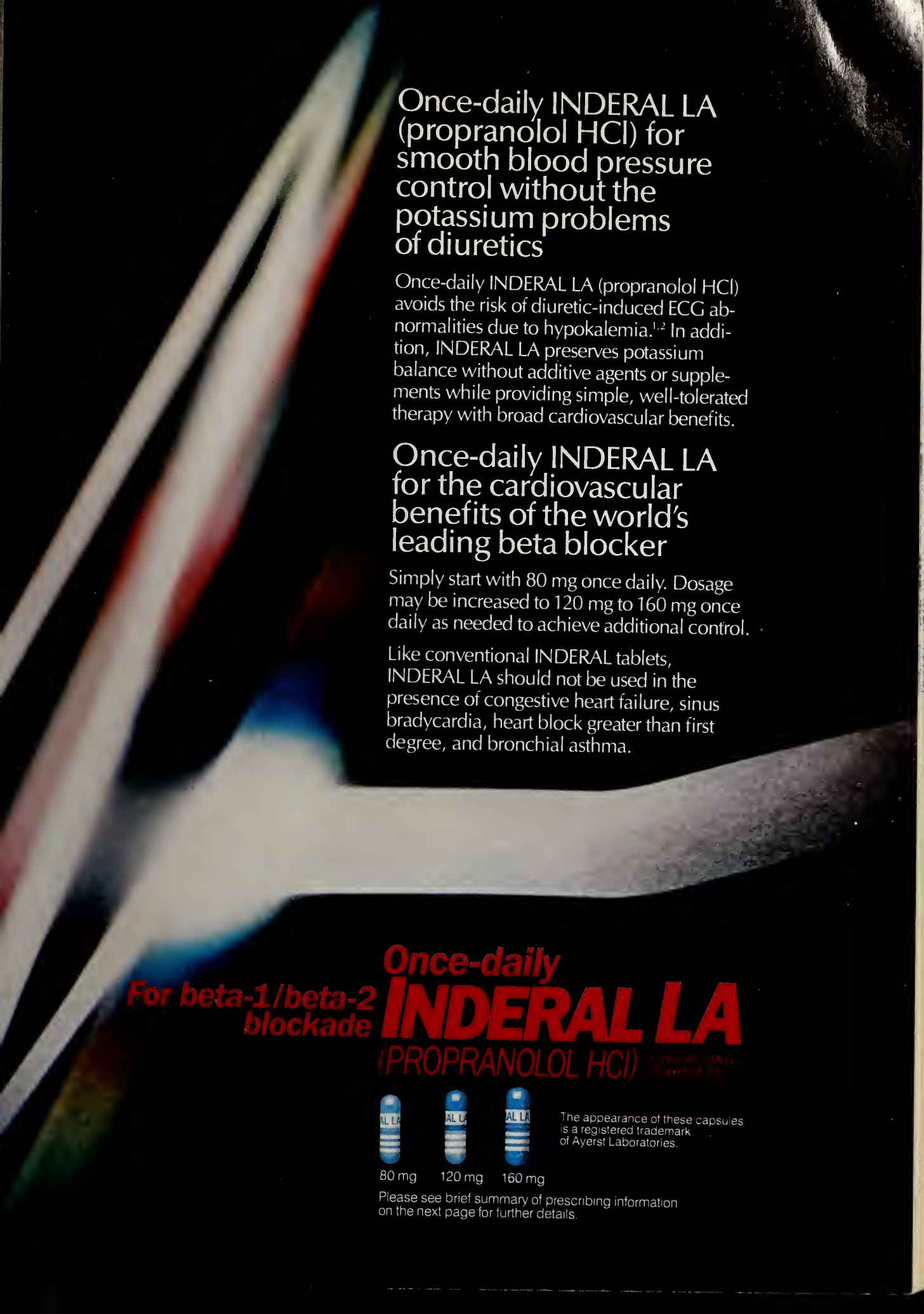
UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

Right from the start in hypertension...


Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics
Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[1,2] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.
Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker
Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.
Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.
For beta-1/beta-2 blockade
Once-daily
INDERAL LA
(PROPRANOLOL HCl)
The appearance of these capsules is a registered trademark of Ayerst Laboratories.
80 mg
120 mg
160 mg
Please see brief summary of prescribing information on the next page for further details.

"When it comes to cardiovascular medicine, I like to know exactly what my patients are swallowing."

INDERAL® Tablets

BRAND OF PROPRANOLOL HCl

10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands, thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

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New York, N.Y. 10017

(Continued from Page 167)

Clinic & Research Foundation at Sherwood Hall, La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. 14 hrs. Fee: $25-$195. Contact: Bonny A. Mower, Scripps Clinic & Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

October 5—**Allergy of Ears, Nose and Sinuses.** Los Angeles Society of Allergy and Clinical Immunology at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Geri Coldewey, LASACI, 1626 N. Wilcox, #557, Hollywood, CA 90028.

October 16-19—**Rheumatology and Clinical Immunology: An Advanced Course.** UCSF at Hotel Meridien, San Francisco. Wednesday-Saturday. 19 hrs. $225-$375.

October 25—**Current Treatment of Allergy.** PMC at San Francisco. Friday.

ANESTHESIOLOGY

September 7-11—**Case Conference on Clinical Anesthesia.** California Society of Anesthesiologists and Travenol Laboratories at High Sierra Hotel, Lake Tahoe, NV. Saturday-Wednesday. 10 hrs. Contact: Linda P. Londerville, CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo, CA 94401. (415) 348-1407.

September 27-29—**Anesthesia Practice, 1985.** Anesthesiology Educational Foundation at Monterey. Friday-Sunday. 10.5 hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles, CA 90024.

October 17-26—**1985 Post ASA Annual Meeting in Hawaii.** California Society of Anesthesiologists at Hotel Intercontinental, Maui, HI. Thursday-Saturday. 24 hrs. Contact: Linda P. Londerville, CSA, 100 S. Ellsworth, #806, San Mateo, CA 94401. (415) 348-1407.

CANCER

October 21-23—**9th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. 22 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 453-6222.

CARDIOLOGY

August 16-18—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. Fee: $190-295. Contact: Medical Education Resources, 5808 So. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

September 19-21—**Echocardiography Technologist Certification Review.** The Institute for Medical Studies at Los Angeles. Thursday-Saturday. Contact: Kim Stroich, IMS, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 495-4499.

September 21—**Pulmonary Medicine.** UCSF at Fresno. Saturday.

September 26-28—**Cardiology Update, 1985.** American College of Cardiology at Quail Lodge, Carmel. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

September 30-October 4—**Comprehensive Review in Vascular Surgery** UCLA at Miramar Sheraton, Santa Monica. Monday-Friday. 32 hrs.

October 3-5—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday. 17 hrs. $150-$325.

October 4-5—**Mycology Review.** STAN at Stanford. Friday-Satruday. 14 hrs.

October 5—**8th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. Contact: Sandra Rozzen, Northridge Hospital, 18300 Roscoe Blvd., Northridge, CA 91328. (818) 885-5311.

October 25-27—**International Symposium in the Aortic Root.** Scripps Clinic and Research Foundation at Hotel Del Coronado, San Diego. Friday-Sunday. 23 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 453-6222.

EMERGENCY MEDICINE

August 26-30—**Topics in Emergency Medicine.** UCSF at Holiday Inn on Union Square, San Francisco. Monday-Friday. 33 hrs.

September 14-21—**Topics in Emergency Medicine.** International Conferences at Hawaii. One week. 10 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

September 23-27—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD at San Diego. Monday-Friday. 13-33 hrs. $215-$440.

September 24-26—**Postgraduate Institute for Emergency Physicians: Advanced Procedures Laboratory.** UCSD at San Diego. Tuesday-Thursday. 3 hrs. Fee: $250.

October 3-6—**Emergency Medicine: Challenging Clinical Problems.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Thursday-Sunday.

October 4-6—**Update in Emergency Medicine.** Mercy Medical Center at Napa Valley. Friday-Sunday. 10 hrs. $125. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding, CA 96099-6009. (916) 243-2131.

October 16-20—**Traumatic Head Injury.** UCD at Red Lion Motor Inn, Sacramento. Wednesday-Sunday.

(Continued on Page 176)

California Medical Association
Regional Postgraduate Institutes

NEW PROGRAMS

West Coast Counties
Monterey Sheraton
October 24-26, 1985

San Joaquin Valley Counties
Curry Village, Yosemite
April 17-19, 1986

TOPICS

- Practical Dermatology
- Update on AIDS
- Update on Hepatitis
- Current Antibiotic Therapy
- Quackery and Cancer in California
- Diabetes Management
- Cancer Chemotherapy
- Issues in Immunization
- Update for Primary Care Physicians

The content of these programs has been determined by the educational needs of primary care physicians as perceived and translated by the members of the Planning Committee.

***

These programs are accredited for Category One credit for Physicians and Registered Nurses

***

Hotel space is limited — early reservations are suggested.

***

Complete program and hotel information will be sent by return mail.
Use the tear off sheet below or call CMA 415/863-5522. extension 416.

WJ08/85

I plan to attend the following Postgraduate Institute(s):

☐ West Coast Counties
October 24-26, 1985
Monterey Sheraton

☐ San Joaquin Valley Counties
April 17-19, 1986
Curry Village, Yosemite

FEE: $125 for each institute
($200 for Non-CMA members)

Please make check payable to
California Medical Association

Name _____ Specialty _____
Address _____
City _____ Zip _____
Number of years out of medical school _____

Mail to: California Medical Association, 44 Gough Street, San Francisco, CA 94103
Attention: Janice Rigney

A program and hotel reservation form will be sent to you.

BALANCED CALCIUM CHANNEL BLOCKADE!

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

2/84

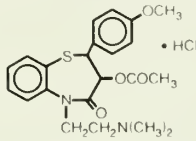
FRANCIS A. COUNTWAY LIBRARY OF MEDICINE

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 2.0 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given, a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered.

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

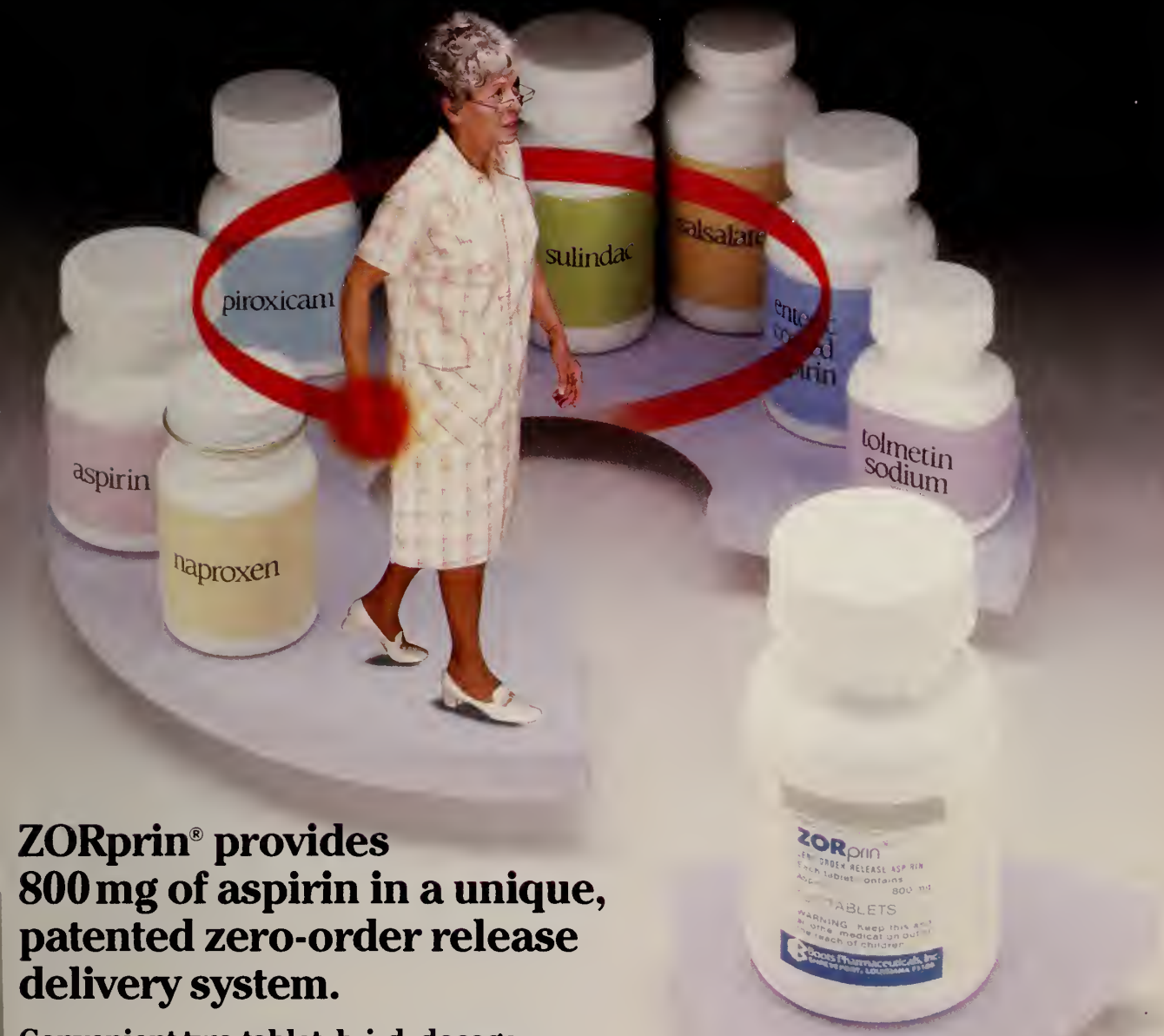
Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC
KANSAS CITY, MISSOURI 64137

Put ZORprin (ASPIRIN) Zero-Order Release in your circle of arthritic therapy



ZORprin® provides 800 mg of aspirin in a unique, patented zero-order release delivery system.

Convenient two-tablet, b.i.d. dosage
- Easy-to-remember regimen improves compliance
- 24-hour pain relief

Efficacy comparable to NSAIs
- Helps reduce morning stiffness and nighttime pain

Side effect profile superior to plain aspirin... comparable to NSAIs
- ZORprin® is economical arthritic therapy
- Prescription only

The ideal method to maintain therapeutic control

Pioneers in medicine for the family

Boots Pharmaceuticals, Inc.
6540 LINE AVENUE, P.O. BOX 6750
SHREVEPORT, LOUISIANA 71106-9989

See brief summary of prescribing information on next page.

ZORprin (aspirin) ZERO-ORDER RELEASE

Before prescribing see complete prescribing information. The following is a brief summary ▫ **INDICATIONS AND USE**: ZORprin® is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of ZORprin® have not been established in those rheumatoid arthritic patients who are designated by the American Rheumatism Association as Functional Class IV, (incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care) ▫ **CONTRAINDICATIONS**: ZORprin® should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. ZORprin® is not recommended for children under 12 years of age; it is contraindicated in all children with fever accompanied by dehydration ▫ **WARNINGS**: ZORprin® should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress the concentration of prothrombin in plasma and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics, concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. While salicylates in large doses have a uricosuric effect, smaller amounts may reduce the uricosuric effect of uricosuric agents ▫ **USE IN PREGNANCY**: Aspirin can cause fetal harm when administered to pregnant women. Aspirin interferes with maternal and infant blood clotting and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Aspirin should not be taken during the last 3 months of pregnancy ▫ **PRECAUTIONS**: Appropriate precautions should be taken in prescribing ZORprin® for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing ZORprin® for those patients with bleeding tendencies or those on anticoagulant drugs. Large doses of salicylates should be avoided in patients with clear evidence of carditis. In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ZORprin® (aspirin) is made a part of the treatment program. Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by reduction in dosage. Salicylates can produce changes in thyroid function tests. Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. Since aspirin release from ZORprin® is pH dependent, it may change in those conditions where the gastric pH has been increased via antacids, gastric secretion inhibitors or surgical procedures ▫ **ADVERSE REACTIONS**: **Hematologic**: Aspirin interferes with blood clotting. Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid ZORprin® Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal**: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from ZORprin® is designed to occur in the small intestine over a period of time. This has resulted in less symptomatic gastrointestinal side effects. **Allergic**: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. The most common allergic reaction to aspirin is the induction of bronchospasm with asthma-like symptoms. Other reactions are hives, rash, angioedema, as well as rhinitis and nasal polyps. Fatal anaphylactic shock, while not common, has been reported. **Central Nervous System**: Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. **Renal**: Aspirin may rarely cause an increase in the severity of chronic kidney disease. **Hepatic**: High doses of aspirin have been reported to produce reversible hepatic dysfunction ▫ **OVERDOSAGE**: Overdosage, if it occurs, would produce the usual symptoms of salicylism, tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Treatment for mild intoxication, emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of saline and sodium bicarbonate or sodium lactate, dextrose solution. In extreme cases, hemodialysis or peritoneal dialysis may be required ▫ **HOW SUPPLIED**: ZORprin® tablets 800 mg, plain, white capsule-shaped tablets. Bottles of 100 tablets ▫ **CAUTION**: Federal Law prohibits dispensing without prescription. Manufactured and distributed by: Boots Pharmaceuticals, Inc. Shreveport, LA, 71106 USA.

Pioneers in medicine for the family

Boots Pharmaceuticals, Inc.
6540 LINE AVENUE, P.O. BOX 6750
SHREVEPORT, LOUISIANA 71106-9989

CONTINUING MEDICAL EDUCATION

(Continued from Page 171)

October 28-November 1—**Postgraduate Institute for Emergency Physicians: Symposium III.** UCSD at San Diego. Monday-Friday. 13-33 hrs. $215-$440.

October 30—**Postgraduate Institute for Emergency Physicians: Advanced Procedures Laboratory.** UCSD at San Diego. Wednesday. 3 hrs. $250.

INTERNAL MEDICINE

August 18-23—**New Advances in Internal Medicine: Clinical Applications.** UCD at Napa Valley. Sunday-Friday.

August 31-September 3—**Advances in Internal Medicine Postgraduate Course 1985.** UCSD at Sheraton Harbor Island East, San Diego. Saturday-Tuesday. 25 hrs.

September 12-14—**Internal Medicine at the Monterey Jazz Festival.** UCI and Institute for Medical Studies at Monterey. Thursday-Saturday. 12 hrs. Contact: Kim Stroich, Institute for Medical Studies, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 495-4499.

September 20-21—**Internal Medicine Symposium.** Southern California Permanente Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. Contact: Judy Harrison, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

September 30-October 2—**Frontiers in Clinical Nephrology 1985.** UCLA at Mission Inn, Sonoma. Monday-Wednesday. 22 hrs. $395.

October 7-9—**GI Board Review.** USC at Los Angeles. Monday-Wednesday. 21.5 hrs.

October 12-19—**Gastroenterology: A Review.** International Conferences at Hawaii. One week. 20 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

October 17-19—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday.

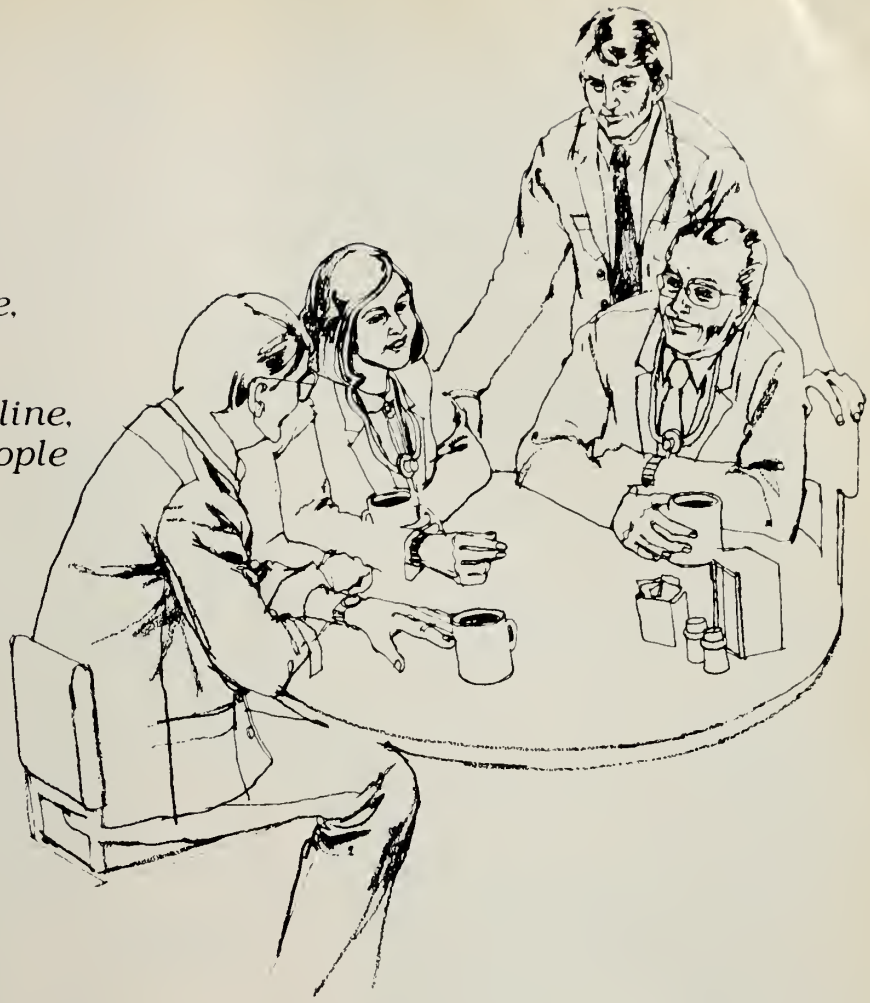
October 17-20—**Practical Advances in Internal Medicine.** UCD at Napa Valley Holiday Inn, Napa. Thursday-Sunday.

October 18-20—**Practice Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** Continuing Medical Education Associates at Vacation Village, San Diego. Friday-Sunday. 20 hrs. $295. Contact: J. Shiller, CMEA, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

OB/GYN

September 28—**Clinical Ultrasound—Update and Ob/Gyn.** Sacramento Radiology Research and Edu-

(Continued on Page 180)



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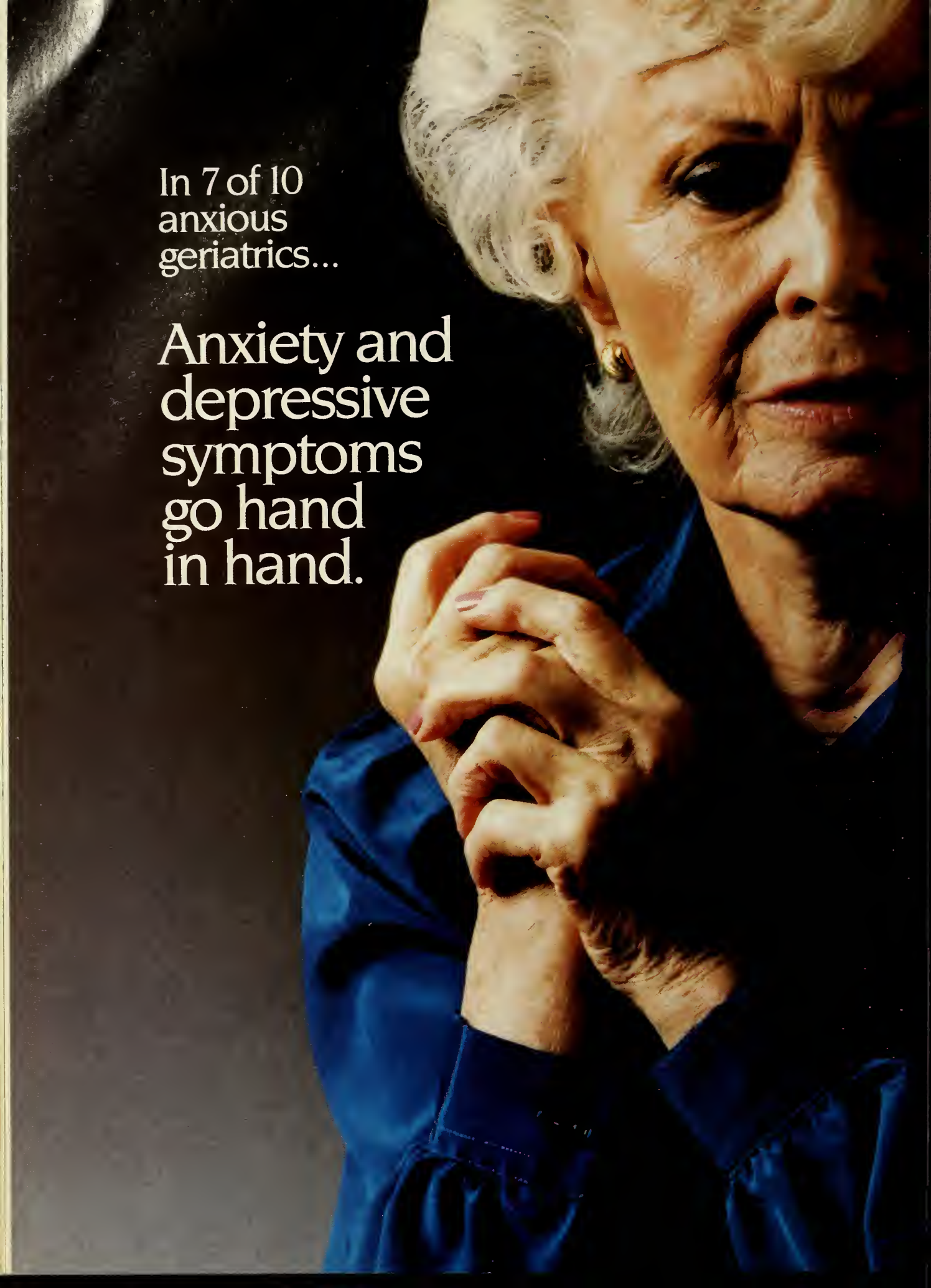
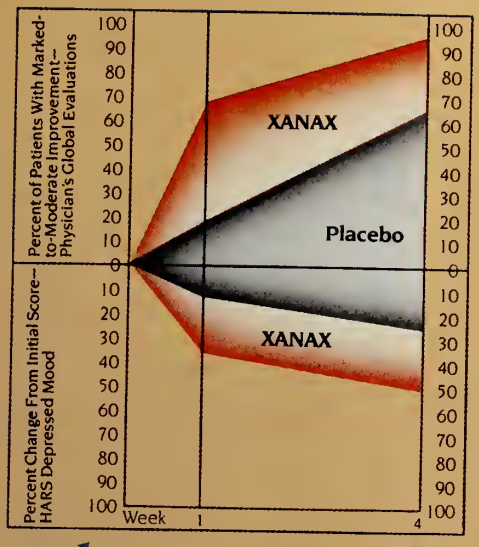

In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax rapidly relieves anxiety with depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100–112.

Xanax® 0.25 mg Tablets
alprazolam C IV

©1984 The Upjohn Company

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-3-S

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

CONTINUING MEDICAL EDUCATION

(Continued from Page 176)

cation Foundation at Sacramento. Saturday. 6 hrs. Fee: $50-$75. Contact: SRREF, PO Box 19184, Sacramento, CA 95819.

October 28-November 2—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** Memorial Medical Center at Sheraton, Newport. Monday-Saturday. 42-46 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

OPHTHALMOLOGY

September 29-October 4—**American Academy of Ophthalmology Annual Meeting** at San Francisco. Sunday-Friday. Contact: AAO, PO Box 7424, San Francisco, CA 94120. (415) 921-4700.

PEDIATRICS

October 2-3—**42nd Annual Brenneman Memorial Lectures.** American Academy of Pediatrics at Los Angeles. Wednesday-Thursday. 13 hrs. $185. Contact: Eve Black, PO Box 2022, Inglewood, CA 90305.

October 11-12—**27th Kaiser-Permanente Pediatric Symposium.** Southern California Permanente at Town and Country Hotel, San Diego. Friday-Saturday. Contact: Lilia M. Guerrero, Dept. of Clinical Services, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 26-November 2—**10th Annual Pediatrics for the Practitioner.** Memorial Medical Center at Mauna Kea Beach Hotel, HI. Saturday-Saturday. 20 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

PSYCHIATRY

September 13-15—**Guided Imagery (Advanced).** Institute for the Advancement of Human Behavior at San Francisco. Friday-Sunday. 18 hrs. Fee: $245-$350. Contact: IAHB, 4370 Alpine Rd., Ste. 205, Portola Valley, CA 94025. (415) 851-8411.

October 18-20—**Mind of a Murder.** Southern California Psychiatric Society at Hotel Del Coronado, San Diego. Friday-Sunday. 9 hrs. $95. Contact: Sharon Karp, 2001 S. Barrington Ave., #214, Los Angeles, CA 90025. (213) 477-1041.

RADIOLOGY

August 27-30—**Radiology Conference.** Northern California Radiology Society at Napa Valley. Tuesday-Friday. 20 hrs. Fee: $275-$345. Contact: Sacramento Radiology Research & Education Foundation, PO Box 18184, Sacramento, CA 95819.

September 1-5—**2nd Annual Radiology and Biology of Physics.** UCSD at Town and Country Hotel, San

Diego. Sunday-Thursday. 28 hrs. Fee: $375. Contact: Ryals and Associates, PO Box 610203, DFW Airport, TX 75261. (214) 659-9590.

September 3-6—**The Physics and Biology of Radiology: A Review Course for Diagnostic and Therapy Residents.** UCSD at Town and Country Hotel, San Diego. Tuesday-Friday. 24 hrs. Contact: Ryals and Associates, PO Box 610203, DFW Airport, TX 75261. (214) 659-9590.

September 5-8—**Physics of Diagnostic Radiology.** UCD at Davis. Thursday-Sunday. 25 hrs.

September 7—**12th Annual Radiology Symposium: Endourology/Abscess Localization and Ectopic Pregnancy.** Southern California Permanente at Airport Hilton, Los Angeles. Saturday. Contact: Lilia M. Guerrero, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 3-5—**3rd Biannual Symposium in Cardiac Imaging.** The Institute for Medical Studies at Hotel Meridien, San Francisco. Thursday-Saturday. 18 hrs. Contact: Kim Stroich, IMS, 20131 Town Center Drive, #215, Laguna Nigel, CA 92677. (714) 494-4499.

October 19-20—**Head and Neck Radiology: Advanced Techniques in Diagnostic Imaging.** UCSF at Hyatt Regency, San Francisco. Saturday-Sunday. 12 hrs. $175-$275.

October 19-20—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Hegency, San Francisco. Saturday-Sunday.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency, San Francisco. Monday-Friday. 31 hrs. $375-$475.

October 28-November 1—**10th Annual San Diego Postgraduate Radiology Course.** UCSD at San Diego. Monday-Friday. $425. Contact: Mary J. Ryals, PO Box 610103, Dallas Fort Worth Airport, TX 75261. (214) 659-9590.

SPORTS MEDICINE

October 24-25—**Sports Medicine Hawaii: International Endurance, Sports and Fitness Symposium II.** UCI at Sheraton Royal Waikoloa, Kona, HI. Thursday-Friday. 16 hrs. $90-$240. Contact: J. Massimino, MD, 896 Town and Country Office Park, Orange, CA 92668. (714) 989-3432.

SURGERY

August 16-18—**Summer Conference on Allergy, Rheumatology and Orthopedic Surgery.** Scripps Clinic and Research Foundation at La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. 14 hrs. Fee: $25-$195. Contact: Bonny A. Mower, Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

September 4-7—**Superficial Anatomy and Cutaneous Surgery for Dermatologists.** UCSD at San Diego. Wednesday-Saturday. 22.5 hrs.

September 18-21—**A Cementless 'Revolution' in Joint Replacement, 1985.** UCLA Extension at Los Angeles. Wednesday-Saturday. 27 hrs. Fee: $100-$475. Contact: UCLA Extension, PO Box 24901, Los Angeles, CA 90024. (213) 825-7186.

September 21-22—**Annual Scientific Symposium: Controversies in Surgery.** International College of Surgeons, Southern California Division, at Las Vegas Hilton, Las Vegas, NV. Saturday-Sunday. 3 hrs. Contact: (213) 483-1581, x. 251.

October 19-20—**Anterior Cruciate Ligament.** Memorial Medical Center at Long Beach. Saturday-Sunday. 10.5 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

October 19-26—**7th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott Hotel, HI. Saturday-Saturday. 36 hrs. $875.

OF INTEREST TO ALL PHYSICIANS

August 17-18—**Clinical Hypnotherapy for Professionals.** UCLA Extension at Los Angeles. Saturday-Sunday. Fee: $95. Contact: UCLA Extension, PO Box 24901, Los Angeles, CA 90024. (213) 825-2301.

August 17-23—**Fine Needle Aspiration.** UCSF at Marriott Biltmore, Santa Barbara. Saturday-Friday. Fee: $525.

August 21-25—**26th Annual Advanced Seminars in Dermatology.** UCSD at Sheraton Harbor Island West, San Diego. Wednesday-Sunday. 16 hrs.

September 9-13—**Primary Care.** UCSF at Sir Francis Drake, San Francisco. Monday-Friday.

September 11-12—**Perspective on Clinical Nutritution (1985 Postgraduate Course).** American Society for Parenteral and Enteral Nutrition at Cathedral Hill Hotel, San Francisco. Wednesday-Thursday. Contact: ASPEN, 8605 Cameron St., Ste. 500, Silver Spring, MD 20910. (301) 587-6315.

September 12-13—**Monoclonal Antibodies: Diagnostic & Therapeutic Uses in Tumors and Transplantation.** UCD at Hyatt Union Square, San Francisco. Thursday-Friday.

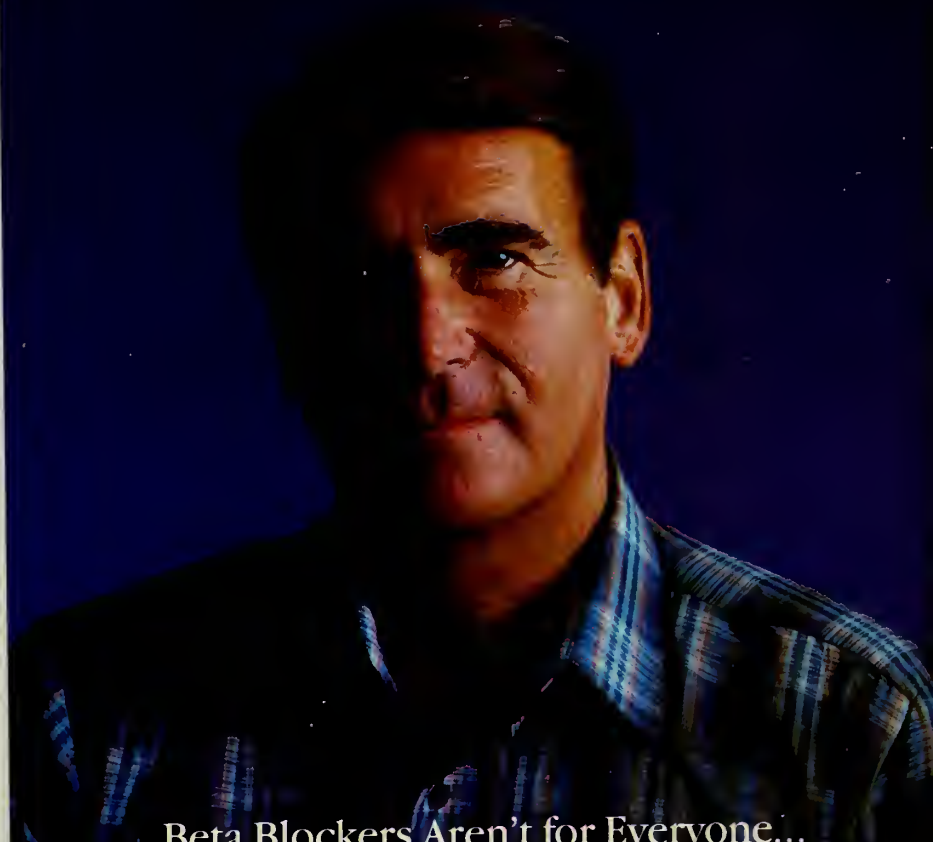
September 12-14—**Kids Have Bones, Too.** UCD at Beverly Garland, Sacramento. Thursday-Saturday.

September 18-19—**53rd Annual Fall Symposium.** American Heart Association at Wilshire Blvd. Hilton, Los Angeles. Wednesday-Thursday. 13 hrs. Fee: $100-$185. Contact: Marianne Joyce, AHA, Greater Los Angeles Affiliate. (213) 385-4231.

(Continued on Page 282)

In Hypertensives Over 50, Diuretics Are Preferred

The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics as the favored monotherapy in patients over 50 years of age, regardless of sex or race.



Beta Blockers Aren't for Everyone...

For Hypertensive Patients* Over 50

PRESCRIBE

DYAZIDE®

25 mg Hydrochlorothiazide/**50 mg** Triamterene/SKF

Used with Confidence for over 19 Years

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ:L39

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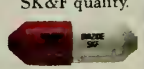
The unique red and white Dyazide® capsule: Your assurance of SK&F quality.



Clinical Investigation

Comparison of Flow Rates for Standard and Large-Bore Blood Tubing

KENNETH V. ISERSON, MD; ALAN K. REETER, MSEE, CCE, *and* ELIZABETH CRISS, RN, *Tucson*

One of the clinically significant rate-limiting components in even the fastest of intravenous (IV) fluid systems is the tubing connecting the IV catheter to the IV solution container. We evaluated the effect large-bore tubing has on reducing this limitation on fluid flow, measuring gravity and pressurized flow in standard and large-bore tubing alone and when each was connected to an 8 French and 12-, 14- and two types of 16-gauge catheters. When combined with an 8 French catheter, large-bore tubing produces a 126% increase in flow under gravity and a 90% increase under pressure. The improvement with the large tubing was less significant as the catheter size decreased. Studies in normovolemic adult volunteers achieved similar results. Large-bore blood tubing and large-bore catheters should be used in all situations where the need for rapid fluid replacement is contemplated.

(Iserson KV, Reeter AK, Criss E: Comparison of flow rates for standard and large-bore blood tubing [Clinical Investigation]. West J Med 1985 Aug; 143:183-185)

The need for rapid volume replacement in cases of traumatic or nontraumatic exsanguination is well recognized.[1-4] This recognition has produced a variety of methods designed to quickly infuse fluids intravenously (IV) to such patients.[1-7] However, one of the rate-limiting components in even the fastest system is the tubing connecting the catheter to the IV bag. Recently, a large-diameter IV tubing has become commercially available in the United States.

We compared the flow rates of this large-bore blood tubing with standard IV blood tubing. The results indicate that the large-bore tubing is a significant new tool for hypovolemic resuscitation. Clinical trials using the largest catheter-tubing combination in normovolemic human subjects also confirm this conclusion.

Methods

Large-bore blood tubing (Fenwal Laboratories, Deerfield, IL 60015, #4C2194) and standard blood tubing (Delmed Y-Blood Solution Set, #03-122-00) were studied. The large-bore tubing had an internal diameter of approximately 3.66 mm (11 French) and was 220 cm long. The standard tubing had an internal diameter of 3 mm (9 French) and was 230.5 cm long.

Utilizing gravity and a constant pressure of 300 mm of mercury, flow rates were measured for each type of tubing. The rates were determined for each type of tubing alone and for each type of tubing in combination with five catheters: 8 French (Universal Medical Instrument, Inc, Ballston Spa, NY 12020), 12 gauge (Vygon, Laboratoires Pharmaceutiques, BP-7 95440 Ecoven, France), 14 gauge (Travenol Laboratories, Deerfield, IL 60015), 16 gauge (Vygon) and 16 gauge (Travenol). Each measurement began with a vertical distance of 91.44 cm (3 ft) between the fluid level in the IV bag and the catheter tip. A glass graduated cylinder (KIMAK, TD 20°C, #20024) was used for measurement. A flow rate was calculated for each tubing and tubing-catheter combination by timing the flow of a series of three 400-ml aliquots of 5% dextrose in water USP.

Following these in vitro experimentations, three normovolemic male volunteers were given 1,000 ml of fluid in two timed 500-ml aliquots using the 12-gauge-large-bore tubing combination under pressure. The basilic or cephalic vein in the antecubital fossa was the site of placement for the catheter.

Results

We measured the gravity flow rates for the standard blood tubing and large-bore tubing alone and when each was connected to 8 French and 12-, 14-, and two types of 16-gauge catheters (Table 1). The standard tubing alone produced a mean flow rate of 173 ml per minute and rates of 171, 169,

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134, 102 (Vygon) and 88 (Travenol) ml per minute, respectively, when combined with the various catheters. The large-bore tubing alone had a rate of 414 ml per minute and with the catheters produced mean flow rates of 387, 333, 211, 136 (Vygon) and 110 (Travenol) ml per minute, respectively.

We also measured the flow rates under pressure using the same tubing and tubing-catheter combinations. The flow rates with the standard tubing and tubing-catheter combinations were 571, 545, 522, 429, 324 (Vygon), and 270 (Travenol) ml per minute, respectively. The flow rates for the large-bore tubing and tubing-catheter combinations were 1,263, 1,043, 889, 500, 369 (Vygon) and 333 (Travenol) ml per minute, respectively.

The measured flow rates using the 12-gauge catheter and large-bore tubing under pressure in the human subjects averaged 848 ml per minute (range, 818 ml per minute to 870 ml per minute).

Discussion

The steady laminar flow rate of incompressible fluid through circular tube is proportional to the fourth power of the radius, as described in Poiseuille's law:

$$Q = \frac{\pi r^4 (\Delta P/L)}{\eta 8}$$

where Q = rate of flow, r = tube radius, $\Delta P/L$ = pressure gradient and η = dynamic fluid viscosity.

Ideally, then, without a catheter the larger tubing should have a flow rate 2.2 times that of standard IV tubing. In our tests using a pressure of 300 mm of mercury, the large-bore tubing alone actually did produce an increased flow rate 2.2 times that of the small tubing. In the gravity tests, however, it produced an increased flow rate 2.4 times that of the small tubing. While seemingly paradoxical, two factors came into play. First, the flow in the small tubing, because of its narrow diameter, was almost certainly inhibited by increased turbulence. Second, in the pressurized systems the flow rate was probably not as great because increased fluid velocity alone tends to create more turbulence. Increased turbulence causes the system to perform below theoretic predictions.

When combined with the largest catheter, the large-bore tubing improved the flow rate by 126% under gravity and 90% under pressure. While the improvement in flow rates with the large-bore tubing is substantial, it is less than that predicted by Poiseuille's law. Yet it is a clinically significant improvement for a severely hypovolemic patient.

When small catheters are used with the large-bore tubing, they become the primary limiting factor for fluid flow. As catheter size was decreased in this study, the effect of tubing size became less significant. With the smallest catheter the large-bore tubing improved the flow rate by only 25% under gravity and 23% under pressure. Therefore, using the large-bore tubing with these catheters is not a cost-effective alternative.

The significant differences among the various brands of 16-gauge catheters are consistent with prior reports.[4,5]

Significantly, no appreciable differences were found in vitro between the flow rates of the peripheral 12-gauge and the central 8 French catheters which, in fact, have a very similar internal diameter. Therefore, percutaneous peripheral insertion of the 12-gauge catheter should be a suitable alternative to the potentially dangerous central vein catheterization.[8]

In normovolemic human subjects, a flow rate decrease consistent with fluid flow theory (Poiseuille's law) occurred when using the 12-gauge catheter-large-bore tubing combination under pressure. With an estimated backpressure of 15 to 18 mm of mercury in the peripheral venous system, there was a proportional decrease in fluid flow. This decrease is expected because of a linear relationship between the pressure gradient (ΔP) and the rate of fluid flow. Despite this 5% to 6% decrease in flow rate, a clinically significant amount of fluid was safely and quickly infused with this combination.

Based on the results of this study, it seems clear that large-bore blood tubing and a large catheter should be used in

TABLE 1.—*Mean Times for Tubing and Tubing-Catheter Combinations*

	Fenwal Large-Bore Tubing		*Delmed Y-Blood Solution Set*		*Increase in Flow With Large-Bore Tubing (%)*	*P value*
	Min:sec	*(ml/min)*	*Min:sec*	*(ml/min)*		
Tubing Alone (No catheter)						
With pressure	:19	(1,263)	:42	(571)	121	<.05
Without pressure	:58	(414)	2:19	(173)	139	<.05
8 Fr UMI						
With pressure	:23	(1,043)	:44	(545)	90	<.05
Without pressure	1:02	(387)	2:20	(171)	126	<.05
12 gauge Vygon						
With pressure	:27	(889)	:46	(522)	70	<.05
Without pressure	1:12	(333)	2:22	(169)	97	<.05
14 gauge Travenol						
With pressure	:48	(500)	:56	(429)	17	<.05
Without pressure	1:54	(211)	2:59	(134)	57	<.05
16 gauge Vygon						
With pressure	1:05	(369)	1:14	(324)	14	<.05
Without pressure	2:57	(136)	3:56	(102)	33	<.05
16 gauge Travenol						
With pressure	1:12	(333)	1:29	(270)	23	<.05
Without pressure	3:38	(110)	4:32	(88)	25	<.05

Fr = French, UMI = Universal Medical Instrument

all situations where the need for rapid fluid replacement is contemplated. In addition, our data suggest that the use of the peripheral 12-gauge catheter may be an alternative to the more complication-prone large central catheter.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Heart-Lung Transplantation

QUESTION:

Is heart-lung transplantation considered acceptable medical practice or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Chest Diseases, General Surgery and Internal Medicine and the Ad Hoc Committee of Organ and Tissue Transplantation, heart-lung transplantation cannot be considered standard medical practice at the present time. This procedure is still under investigation and should be restricted to those institutions that have shown the necessary skills, resources (both clinical and research) and institutional commitment to manage the patient's total preoperative and postoperative care. The number of such centers is few.

General advances in immunosuppression and patient selection have contributed to the successful short-term survival of the small number of patients who have received heart-lung transplants. However, a larger number of patients is required to confirm the preliminary results and document long-term survivial.

To date, patients with irreversible pulmonary vascular disease either of a primary nature or secondary to cardiac defects have been the best candidates for heart-lung transplantation.

Risk Factors in Stroke

PIERO MUSTACCHI, MD, *San Francisco*

In the United States, stroke accounts for 160,000 annual deaths; only 16% of the 1.8 million stroke survivors are fully independent. The incidence of stroke increases with age. Hemorrhagic strokes outnumber ischemic strokes before age 15. Japanese men in this country have a lower stroke mortality than their age peers in Japan. Excessive stroke mortality for US nonwhites may not be entirely due to the greater prevalence of hypertension among blacks. Hypertension emerges as the single most powerful and reversible risk factor in stroke and for survival after stroke. Impaired cardiac function is the second most important precursor of stroke. The recurrence of stroke in survivors is high. The frequency of completed stroke is high in persons with transient ischemic attacks, but not in those with asymptomatic carotid bruits. Other reversible risk factors are smoking, the use of oral contraceptives, alcoholic excess, a low level of physical activity, blood hyperviscosity and drug abuse.

(Mustacchi P: Risk factors in stroke. West J Med 1985 Aug; 143:186-192)

From 13% to 20% of the cardiac output goes to the brain,[1] an organ that represents only 2% of total body weight.[2] Cerebral blood flows normally at a rate of 40 to 45 ml per 100 grams of brain per minute. Considerable reduction in flow can occur before a deficit becomes clinically significant. The ischemic tolerance of neural tissue is proportional to the severity and duration of flow reduction.[3] At zero flow (cardiac arrest), this tolerance is about four minutes.[4] A blood flow of 18 ml per 100 grams per minute at an arterial carbon dioxide pressure of 40 torr can temporarily sustain a normal electroencephalogram.[3] Electroencephalographic changes and presumably ischemic symptoms develop at blood flow rates below 17 ml per 100 grams per minute.[3] A further decrease in flow to less than 10 ml per 100 grams per minute results in permanent brain tissue infarction.[5]

The current definition of stroke stipulates that the focal diagnostic neurologic deficits such as hemiparesis, aphasia or homonymous hemianopia be of abrupt or rapid onset; if not fatal, the deficit should last more than 24 hours. The definition also specifies that the vascular origin be limited to either thrombotic or embolic occlusion of a cerebral artery or to spontaneous rupture of a vessel resulting in intracerebral or subarachnoid hemorrhage. The definition excludes changes due to vascular lesions of clearly traumatic, neoplastic or infectious orgin.

Although mortality from stroke has been steadily declining,[6-14] it still accounts for 16% of all deaths in the United States.[15] In addition to the 160,000 annual stroke deaths, more than ten times as many (some 1.8 million persons) survive stroke with varying levels of residual disability.[15] Among the survivors, cerebral infarction reduces the proportion of those who were completely independent from 57% before infarction to 16% after infarction.[13] Aphasia alone is an important residual incapacity in 10%.[16]

General Risk Factors

Developmental Factors

Intracranial hemorrhage. Intracranial hemorrhage that occurs later in life can be due to bleeding "berry" aneurysms.[17] That many aneurysms become symptomatic around age 20 or later suggests that unidentified developmental factors are at play. A statistically valid association links berry aneurysms to coarctation of the aorta and to polycystic kidneys.[18] Subarachnoid hemorrhage was the cause of death in 22% in a study of persons with polycystic kidneys.[19]

Intracranial hemorrhage, whether subarachnoid or intracerebral, may be the first manifestation of atrioventricular malformations that had been silent until early maturity. Bleeding may follow as late as a decade after an initial convulsive seizure suffered during early adolescence.

When developmental defects lead to asymmetric growth, the smaller vessels are more likely to occlude. Of 17 patients with severe asymmetric carotid stenosis, 13 had greater stenosis on the side of the smaller vessels.[19]

Hemorrhagic strokes. Hemorrhagic strokes outnumber ischemic strokes 3:1 in children younger than 15 years, with a

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combined average annual incidence rate of 2.52 per 100,000.[20] After maturity the reverse is true.[21,22] The incidence rate for stroke increases progressively with age[13,23-25] as atherosclerotic plaques and internal thickness of the basilar artery and the anterior cerebral arteries increase. In the anterior cerebral arteries, the onset of the first atherosclerotic plaques lags by about ten years behind similar formations in the basilar artery.[26]

At birth, elastin in the arteries of the circle of Willis and its large branches is concentrated in the internal elastic layer, in contrast to muscular arteries of other organs whose media and adventitia contain abundant elastic fibers in the outer layer.[27] Increasing amounts of elastic tissue can be found in the external layer of the cerebral arteries until age 2. Thereafter, the density of the elastic fibers seems to decrease until, after age 30, few fibers are still visible. This age-related change in proportion of elastin has been attributed to altered biochemical composition indicative of a concomitant dysfunction.[27]

Sex

Coronary heart disease affects predominantly men, but the sex differential is not so pronounced in cases of stroke.[6,10,28-31] In some age groups and in American blacks,[32] there is a slight excess in the incidence of stroke in women.

Race

Mortality in Japanese and US nonwhites of all ages from vascular lesions of the nervous systems exceeds that of US whites at all ages.[32] Studies of emigrant Japanese suggest that the observed excess reflects environmental rather than genetic factors. American-Japanese men tend to have a lower stroke mortality than their peers in Japan.[33-35] Native Japanese men are significantly more likely to have intraparenchymal arteriosclerosis and cerebral infarction than Hawaiian Japanese.[36] Because the Japanese migration to Hawaii and California occurred mainly between 1880 and 1924, it is of interest that stroke mortality in American-Japanese had dropped nearly to the levels for whites by 1960, whereas their mortality from coronary heart disease remained intermediate.[35]

Nonwhite mortality from cerebrovascular diseases in the United States for persons aged 35 to 74 years has been about twice that of whites.[11,37] The greater prevalence of hypertension among blacks remains a mystery, as the higher rates could be attributed to incorrect death certification in states underserved by physicians,[38] or to underenumeration of the black population by census takers.[39]

Familial Clustering

Parental deaths from stroke,[40] cardiovascular-renal disease[41] or any cause[42] are overrepresented among stroke victims. Hypertension and cerebrovascular disease are significantly more frequent in monozygotic than in dizygotic twins of the same sex.[43]

Secular Trends

The past four revisions of the *International Classification of Diseases* introduced an element of uncertainty in the interpretation of long-term trends of stroke mortality.[6-8,28,44] Studies limited to data collected after the 1968 (most recent) revision concur in a downward mortality trend,[8,10] a pattern that emerges also from separate analyses of the four chronologic periods corresponding to the fifth through the eighth revisions.[11] The decline in stroke mortality that accelerated around the late 1960s[9,11,12] or the early 1970s[45] may even have been underestimated. Epidemiologic evidence indicates that the decline in mortality reflects a real decrease in stroke incidence.[16,45] The reduction in mortality for major cardiovascular diseases since 1965 far exceeds what could reasonably be explained by the decline in the changing autopsy rate since then.[46]

The reasons for the decline are unclear,[47] as it started long before effective antihypertensive therapy became widely available. An attractive hypothesis has correlated these changes in mortality with the declining use of salt.[48] If so, the changes in dietary habits made possible by the introduction of refrigeration and deep freezing may have proved one of the most important contributions to preventing stroke.[49]

Specific Risk Factors

Hypertension

Fixed and systolic hypertension. Hypertension emerges from prospective studies in Framingham (Massachusetts),[50,51] Chicago,[52] Honolulu,[53] Rochester (Minnesota),[54] Finland[55] and Japan[23] as the most common precursor of atherothrombotic brain infarction. The risk increases with elevated systolic and diastolic values,[37] the relationship being almost linear independently of age and sex.[51]

Elevated systolic pressure was highly predictive of subsequent stroke, even when not associated with diastolic elevations. Blood pressure values above 140/90 mm of mercury were recorded in all but 10 of the 105 stroke victims identified during the initial 18 years of the Framingham study. The normotensive persons who had contributed the ten cases of stroke had only one fourth of the stroke risk of their hypertensive counterparts.[51] Hypertension is a powerful predictor of atherosclerotic brain infarction when other factors such as gout, diabetes mellitus and obesity are excluded.[30] Systolic blood pressure values discriminated between susceptible and nonsusceptible persons and systolic and diastolic values used together.[30] In a retrospective study of the stroke mortality of former university students,[41] decedents had registered higher mean systolic and diastolic blood pressures when in college, and significantly more persons who had died of stroke (45%) than controls (31%) had had systolic blood pressure levels above 130 mm of mercury.[41] Japanese data have shown a correlation of systolic and diastolic hypertension and mean arterial pressure with the risk of stroke and that increasing values increase the risk for cerebral hemorrhage and cerebral infarction.[23] In cases of hypertension, the risk for atherothrombotic stroke is essentially the same as for hemorrhagic stroke.[33]

The contribution of hypertension to the risk of stroke is independent of arterial rigidity.[56] Oscillometric finger recordings in the Framingham study of 1,825 consecutive persons graded the depth of the dicrotic notch from absent to pronounced. Because the dicrotic notch is the combined result of rebound elastic recoil after aortic valve closure and such factors as the tone of smaller vessels and peripheral vascular resistance, peripheral vasoconstriction may cause the incisura to disappear. In the absence of peripheral vasoconstriction, aortic valve disease or heart failure, the incisura is largely a

reflection of arterial elasticity and arteriolar tone. Regression analysis of stroke incidence on age, systolic pressure and pulse-wave configuration indicates that the contribution of the pulse-wave is not significant, whereas that of systolic pressure has a high coefficient of correlation. This relationship obtains even though the elastic tissue in the arterial walls diminishes with age and contains more calcium, so that fewer aging persons have a normal pulse-wave tracing.

In persons older than 30 years, isolated systolic hypertension cannot be considered an innocent concomitant of aging inelastic arteries[57] but rather an often-neglected precursor of stroke,[56] hypertensive cardiac failure, coronary heart disease and occlusive peripheral arterial disease.[57] In monkeys, experimentally induced aortic coarctation resulted in systemic hypertension and in multifocal brain lesions at the capillary level. The pathologic changes that could be explained by successive episodes of regional ischemia or hyperperfusion (or both) resembled those seen in the brain of hypertensive humans.[58]

Labile hypertension. In contrast to the gravity of labile diabetes mellitus, labile hypertension is generally viewed either as the relatively benign manifestation of an exaggerated stress response or, at worst, a possible prelude to "fixed" hypertension.[59] Thus there is the tendency to disregard an elevated initial blood pressure reading and to repeat the measurement after the patient is relaxed.

In the Framingham cohort, hypertension was designated by two pressure determinations exceeding 160/95 mm of mercury. Normal tension was defined by values consistently below 140/90 mm of mercury and intermediate readings were considered borderline. It was found that higher pressures were more labile than lower ones, so that persons with fixed hypertension had more labile pressures than those with so-called labile hypertension. Lability also increased with age. For any given average pressure, the risk of cardiovascular events was unaffected by the degree of variability of the pressure. In other words, the higher the average reading, the greater the risk of cardiovascular complications. Rather than disregarding a single hypertensive reading and drawing reassurance from a subsequent normal basal pressure, to identify patients at risk for cardiovascular complications, one should rely on the average of several readings preferably taken on more than one occasion.[60]

Effect on prognosis. In prospective studies in the United States and Canada, survival after stroke was shorter in persons who had hypertension before stroke developed.[61,62]

Effect of treatment. In an Australian study based on regular biannual health screening of a small township, better control of blood pressure was associated with lesser stroke mortality in men aged 50 years and older, but not in women.[63] In a US double-blind study, only 6 cases of stroke occurred among hypertensive persons receiving antihypertensive drugs, whereas 25 cases of stroke occurred in the comparison group receiving a placebo.[64] The study also showed that stroke had occurred in patients whose diastolic pressure had not been reduced below 100 mm of mercury.[64] A study of 10,000 persons with hypertension in 14 cooperating centers confirmed that clinical control of hypertension protects against stroke,[65] especially in patients younger than 70 years. Among patients admitted to hospital for stroke, two thirds were known to have hypertension[66]; although most (91%) were treated with antihypertensive drugs, in the physicians' judgment, one in four had not been taking medications for two or more days. Almost a third of the study group had had diastolic readings above 105 mm of mercury on at least one occasion, with systolic values exceeding 180 mm of mercury at least once in almost half of them.

In Minnesota, a community hypertension control program increased from 40% to 76% the proportion of persons whose hypertension seemed adequately controlled.[67] These impressive results were associated with a declining incidence of and increased survival in cerebral infarction.[13]

Heart Diseases

After hypertension, impaired cardiac function is the most powerful precursor of stroke and atherothrombotic infarction.[68] Embolic stroke can be a complication of cardiac arrhythmia.

Atrial arrhythmias. Atrial arrhythmias will predispose to left atrial thrombus formation and cerebral embolization. Atrial fibrillation increases the risk of stroke sixfold; in the presence of rheumatic mitral disease, the risk increases 17-fold.[69] The annual incidence of cerebral embolization in the presence of sick sinus syndrome is 7.2%.[70] Atrial arrhythmias were identified during long-term electrocardiographic monitoring in 44% of patients with nonhemorrhagic stroke, twice the percentage in the reference population.[70]

Mitral valve prolapse. This valvular abnormality affects 5% of the general population.[71] It has been associated with the development of focal neurologic signs in young normotensive persons who had no overt coagulation defect and who were not using oral contraceptives.[71,72] Angiograms have suggested an embolic pathogenetic mechanism,[73] possibly mediated via platelet coagulant hyperactivity[74,75] or shortened survival time[76] or by newly recognized links between coagulation and cardiovascular disorders.[72]

Mitral valve prolapse was the only identifiable precursor in 5% to 30% of young adults with otherwise unexplained cerebral infarction,[77-80] but the actual risk of stroke in young adults with asymptomatic mitral valve prolapse seems rather low, possibly of the order of 1 in 6,000 per year.[78] During an observation period of some 3,800 person-years contributed by 760 patients with mitral valve prolapse, only one suffered a stroke,[81] suggesting an annual rate of 1.5 in 6,000. No prophylactic treatment seems warranted in asymptomatic persons with this valvular dysfunction.[78] Among persons with mitral valve prolapse, the prevalence of stroke is four times that observed in the general population.[82]

Hypertensive and atherosclerotic heart disease. The risk for atherothrombotic cerebral infarction is greatest among hypertensive persons with electrocardiographic[23,53] or radiologic evidence of cardiac involvement,[30] reflecting suboptimal cardiac output and reduced cerebral perfusion at the level of severely narrowed vessels.[30] A previous history of myocardial infarction almost trebles the risk of stroke (relative risk = 2.9).[25]

Effect on prognosis. Besides being risk factors, prestroke hypertension, coronary heart disease and congestive heart failure reduce the five-year survival rate for cases of brain infarction from 85% to 35% in men and from 70% to 56% in women.[66] The higher the systolic blood pressure before stroke, the higher the mortality.[62]

Previous Stroke

The Framingham study showed that the recurrence rate among stroke survivors is substantial.[61] Most recurrences are of the type of the previous stroke. Most strokes are atherothrombotic, reflecting the poor survival after the hemorrhagic ones. Men have a higher (42%) five-year cumulative recurrence rate than women (24%). The observed sex difference could reflect better control of hypertension and its complication in women.[61]

Transient Ischemic Attacks

The age-adjusted annual incidence rate for transient ischemic attack (TIA) is 31 in 100,000 in Rochester, Minnesota, where age-specific rates increase with advancing age and show a prominent jump after age 65.[83] In southern California, elderly persons with a history of transient focal or nonfocal cerebral ischemic symptoms carry an increased risk for the development of a completed stroke whether nonfocal symptoms such as spells of dizziness, syncope, vertigo or loss of balance were manifestations of vertebrobasilar ischemia or were caused by impaired cardiac function.[84] Both focal and nonfocal ischemic symptoms were significant and independent predictors of stroke.[84] The cumulative rates of completed stroke were 2.3% among those with focal and nonfocal symptoms, twice the value observed among an asymptomatic comparison group.[84] Patients who have had a TIA are at increased risk for stroke. During the first year after the initial attack, one group had 33 strokes versus the expected 2.[83] A lower relative risk for TIA-related stroke was reported among Hawaiian-Japanese in whom 2 strokes occurred instead of the 0.7 expected.[85]

The observed conditional probability of surviving free of stroke after the first TIA was 62% after five years and 50% after ten years, whereas 90% of the general population would have remained free of stroke for ten years.[83] Regardless of the anatomic source of TIAs, twice as many of the subsequent deaths were due to cardiac causes as to stroke.[86] Because of the accelerated total mortality associated with TIAs, only 25% rather than the expected 50% of a study cohort was still alive ten years after the initial TIA. A similarly accelerated mortality for cardiovascular illness and stroke was shared by a biracial population in Georgia who had symptomatic TIAs.[87] When nonfatal stroke and death were combined as an endpoint, there was no significant difference between the survival curves for vertebrobasilar insufficiency and carotid insufficiency in either men or women.[84]

The risk for ischemic stroke associated with TIAs is most increased in the presence of heart disease[54] and stenosis of large arteries. Stenosis is important mostly as a source of emboli because the arterial lumen of the internal carotid must be reduced by 80% to 90% before there is a significant effect on flow.[88] Both embolic and hemodynamic factors are important in the pathogenesis of TIAs; microemboli are more frequent in the carotids, and hemodynamic factors are of special importance in the vertebrobasilar system.[89]

Asymptomatic Carotid Bruits

As verified by Doppler findings, the hallmark of internal carotid artery stenosis is a high-pitched bruit best heard at the angle of the jaw.[90] In a review of seven prospective studies cumulating 703 persons with asymptomatic carotid bruits, it was concluded that the mean annual rate for completed stroke events is low, probably around 2%.[90] The side of the bruit often does not coincide with the side of the stroke, but this could simply mean that when both carotids are atherosclerotic, a bruit is heard over the least diseased artery.

Because of the low annual risk for stroke in these patients, it is recommended that if a corrective operation is to be done, it should be done in institutions where surgical risks are similarly low—that is, not exceeding 2% or 3% at most.[90] The risk of stroke in the region of a significant but asymptomatic carotid-bifurcation plaque was low (3%) in persons who had undergone contralateral endarterectomy for a TIA or a minor stroke.[91] Stroke was just as likely to develop either in the area of a previously operated carotid artery (5%) or in the vertebrobasilar area (4%).[91]

Other Observations

In a number of studies,[25,31,50,92,93] *impaired glucose tolerance* and *clinical diabetes* were identified as significant and consistent contributors to stroke risk, with an adjusted relative risk of 2.2.[25] At any level of blood pressure, the risk for atherothrombotic stroke is increased in persons with impaired glucose tolerance.[21] Apparently, treating diabetes does not seem to alter the risk for stroke.[94] Thus, it has been concluded that there is no known justification to treat hyperglycemia without evident diabetes if the aim is to reduce the likelihood of stroke.[95] In a study of cases of hyperglycemia with or without diabetes mellitus, the neurologic outcome in stroke was considerably worse, and there was a significantly greater number of stroke-related deaths.[96] In a double-blind, randomized clinical trial, the presence of diabetes mellitus erased the prophylactic effect of aspirin in cases of threatened stroke.[97]

The relationship between *blood lipids* and stroke is weak and uncertain,[95] possibly because patients with higher serum lipid values may not survive to the age at which strokes are common. The Framingham study suggested an association of blood lipid levels with the development of precocious atherosclerotic brain infarction only in men younger than 55.[21] Native Japanese, however, who have a higher stroke mortality than US Japanese, had lower cholesterol levels than Japanese-Americans.[98] Serum cholesterol levels were negatively associated with the risk for intracranial hemorrhage among Hawaiians of Japanese extraction.[31]

In 138 patients who had not suffered a completed stroke but who underwent carotid endarterectomy for extracranial vascular disease, the mean elevation of triglyceride levels was significantly higher than in controls, suggesting that elevated triglycerides rather than cholesterol are a risk factor in extracranial atherosclerotic cerebrovascular disease.[99] Hypertriglyceridemia and elevated pre-β-lipoprotein levels were described in 50 patients with ischemic thrombotic stroke.[100] In men, the presence of elevated serum triglyceride levels doubles the risk for cerebral infarction.[55] Hypertriglyceridemia rather than hypercholesterolemia seems to correlate best with thrombotic stroke occurring before age 50.[100-102] In one study, elevated serum cholesterol values were inversely related to the occurrence of intracranial hemorrhage.[53] Serum triglyceride levels tended to be higher in patients suffering infarction in the distribution of a cortical artery. In them, the ratio of high-density lipoprotein to low-density lipoprotein cholesterol was lower than in patients with strokes traceable

to obstruction of a perforating artery,[103] suggesting that these lipoprotein abnormalities may play a part in the pathogenesis of cerebral cortical infarctions.

Serum *uric acid* elevation has been mentioned as a contributor to the risk for stroke in one study[100] but not in others.[99] Neither persons with gout nor their first-degree relatives were found to have an increased risk for dying of cerebrovascular diseases.[104]

The slight excess in deaths from cerebrovascular diseases reported in smokers of both sexes[105] was verified for men.[55,106-108] Male college students smoking ten or more cigarettes a day were at twice the risk for eventual fatal stroke than those who smoked less or not at all.[42] Although some studies failed to identify a definite relationship between *cigarette smoking* and stroke,[95,105] a relationship probably exists in view of the presence of a dose effect and the reduction in risk that follows cessation of smoking. This emerged from a study of US World War I veterans. Designating 1.0 as the mortality ratio for cerebrovascular diseases among nonsmokers, the following ratios were calculated: current smokers, 1.40; exsmokers, 1.07; pipe and cigar users, 1.06. Among cigarette smokers, a noticeable gradient was associated with increasing daily consumption: fewer than 10 cigarettes, 1.26; 10 to 20 cigarettes, 1.33; 21 to 39 cigarettes, 1.54; two packs a day or more, 1.88.[108] The relationship was stronger in younger age groups and the increased risk associated with smoking appeared to decrease rapidly after cessation.[108]

A collaborative case-control study undertaken in 12 US university hospitals determined that the use of *oral contraceptives* entailed a relative risk of about 9 for thrombotic stroke and of 2 for hemorrhagic stroke.[109] The combined effect of smoking and the use of oral contraceptives selectively increased the risk for subarachnoid hemorrhage.[110] Hypertension compounds the risk for thrombotic stroke among users of oral contraceptives, the relative risk ranging from 3 times baseline value for normotensive users of an oral contraceptive to 14 times in users with severe hypertension.[111]

Alcohol consumption has been positively associated with cerebrovascular diseases,[31,53] the risk increasing with increasing consumption.[112] Acute ethanol intoxication was an immediate antecedent in almost half of 23 consecutive patients younger than 40 years admitted to a Finnish hospital with acute brain infarction.[113] Another Finnish study concluded that a *low level of physical activity* at work was associated with an increased risk for acute myocardial infarction and cerebral stroke in both sexes, even after controlling for age, diastolic pressure, weight and smoking.[114] This observation concurred with the findings of earlier studies of San Francisco longshoremen[115] and of college students[42] indicating that physical activity at work or during leisure time reduced the risk for stroke. Parallel inferences were drawn from a Dutch community-based study that described a dose effect linking inversely the level of physical activity during leisure time with the adjusted relative risk for strokes.[25] The following relative risks were reported: little physical activity, 1.0; light activity, 0.8; heavy physical activity, 0.4. The difference in relative risk between the aggregate of light and heavy physical activity during leisure time and little activity—that is, mainly sitting, was statistically significant.[115]

The literature seems about evenly distributed as to the role of *obesity* in stroke.[25] If anything, the link is weak,[21] as reflected by a relative risk of 1.5[42] to 1.7.[25]

Suboptimal cerebral blood flow, whatever its cause, is potentially harmful in patients at risk for stroke. Thus, under pathologic circumstances, the rheologic properties of blood may become critical,[116] but neither blood viscosity nor the risk for cerebral infarction changes remarkably until the *hematocrit* exceeds 46%, when both increase sharply.[117] The slower flow associated with a higher hematocrit may limit the efficiency of an alternate blood supply through collateral vessels[116] and, distal to a tight stenosis, shear rates may fall and viscosity increase many times. A progressively slower flow will favor thrombus formation.

Fortunately, factors contributing to *hyperviscosity*, such as dehydration, polycythemia and paraproteinemia, can be corrected or at least modified relatively easily. Unfortunately, the same cannot be said about *sickle cell disease*, the cerebrovascular complications of which seem to occur preferentially in children younger than 15 years[118] and where the victim of an initial stroke is more likely to have recurrent cerebrovascular accidents.[118,119] Cerebral infarction in carriers of the sickle cell trait is a rarity[120] and apt to occur only during potentially hypoxic episodes such as status epilepticus or during general anesthesia.

Especially in young adults and adolescents, *drug abuse* is now a significant cause of intracerebral hemorrhage (amphetamines; pentazocine [Talwin] and tripelennamine [Pyribenzamine]; cocaine and phencyclidine); subarachnoid hemorrhage (amphetamines); embolic stroke (pentazocine and tripelennamine, methylphenidate), and ischemic stroke (heroin; pentazocine and tripelennamine; LSD). Direct toxic injury, embolization of foreign matter and pharmacologically mediated vascular change are considered less important etiopathologic pathways than endocarditis and immunologic mechanisms. The latter could explain the frequent polymorphic vascular response and nodose distribution of vascular lesions seen in drug abusers, as well as the delayed onset of stroke after injection or its occurrence after an unusually long period of abstinence.[121] Retrospective observations suggest that in young adults classic *migraine* may be antecedent of stroke.[122]

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Primary Sclerosing Cholangitis— An Immunologically Mediated Disease?

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Primary sclerosing cholangitis (PSC) is an uncommon, chronic disorder characterized by inflammatory fibrosis usually involving the entire biliary tree. The etiology has been unknown, but PSC is closely associated with ulcerative colitis, which coexists in more than two thirds of patients with PSC. In recent studies 3% to 5% of all patients with ulcerative colitis had PSC.

We propose that PSC is, at least in part, an immunologically mediated disease; it is closely associated with human leukocyte antigens B8 and DR3, and circulating autoantibodies to colon and portal tract are frequently present. The anticolon antibody cross-reacts with enteric Escherichia coli. *The disease may possibly be triggered in susceptible patients with ulcerative colitis by immunization with antigens shared between enteric microorganisms and the biliary system.*

(Chapman RWG, Jewell DP: Primary sclerosing cholangitis—An immunologically mediated disease? West J Med 1985 Aug; 143:193-195)

Primary sclerosing cholangitis (PSC) is an uncommon disease characterized by chronic inflammatory fibrosis usually affecting the entire biliary tree, causing beading and stricturing of the bile ducts.[1] The clinical syndromes associated with PSC range from the classic cholestatic presentation with jaundice, pruritus, fever and abdominal pain to cirrhosis and portal hypertension without predominant cholestatic features.[2] In addition, an increasing number of patients are being diagnosed by cholangiography at an asymptomatic stage following the discovery of an elevated serum alkaline phosphatase level.[3]

Etiology

Previous Hypotheses

The etiology of PSC is unknown. Since the original description of PSC by Delbet in 1924,[4] a number of possible factors have been suggested as having a role in pathogenesis. PSC is closely associated with ulcerative colitis, which is found in about two thirds of patients who have PSC.[2,5] Consequently, Warren and co-workers[6] suggested that chronic low-grade portal infection, which may occur in some patients with ulcerative colitis, leads to chronic biliary tract inflammation and fibrosis. This explanation seems unlikely, for the extent of hepatic histologic change is unrelated to the incidence of portal bacteremia and there is no direct evidence for a causal relationship between portal bacteremia and the development of PSC.[7-9]

A second hypothesis is that PSC associated with ulcerative colitis is caused by a reaction to toxic circulating bile acids arising from the diseased colon.[10] In three recent studies, however, no major abnormality in bile acid metabolism was found in patients who had PSC or ulcerative colltis (or both).[11-13]

Ludwig and associates have suggested that PSC may be caused by a virus,[8] as cholangitis and biliary atresia may be induced in weanling mice, primates and, possibly, also in infants after infection with reovirus type 3.[14] There is no evidence, however, to support this interesting concept.

The same group has also proposed that the excess liver copper found in PSC patients may have a role in either initiating or perpetuating the disease process.[8] The latter suggestion seems more likely, as excess liver copper is found in patients with chronic cholestasis from any cause.

New Hypothesis

In a number of recent studies it has been suggested that genetic and immunologic factors are important in the pathogenesis of PSC. These suggestions lead us to propose that PSC is, like primary biliary cirrhosis, an immunologically mediated disease,[15] possibly triggered in genetically predis-

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ABBREVIATIONS USED IN TEXT
HLA = human leukocyte antigen
PSC = primary sclerosing cholangitis

posed persons by a cross-reaction between antibodies to viral or bacterial antigens in the gut and biliary epithelium.

Evidence

Genetic Factors

In a study of 25 patients with PSC, we found a close association between the human leukocyte antigen (HLA) B8 phenotype and PSC.[16] HLA-B8 was present in 60% of patients with PSC, with and without ulcerative colitis, compared with only 25% of 561 controls. Schrumpf and associates have recently found HLA-B8 in 80% of Scandinavian patients with ulcerative colitis and hepatobiliary disease, most of whom had sclerosing cholangitis.[17] HLA-DR3 was found in 70%.[17] We have confirmed these findings in English patients with ulcerative colitis and PSC.[18] Although the prevalence of HLA-B8 and HLA-DR3 is not increased in a population of patients with ulcerative colitis,[19] it seems that patients with ulcerative colitis unfortunate enough to possess HLA-B8 and HLA-DR3 are at an increased risk for the development of PSC.

Further evidence of the importance of genetic factors comes from Quigley and co-workers who reported the cases of three families in whom ulcerative colitis and PSC developed in two members.[20]

The presence of HLA-B8 and HLA-DR3 has been associated with a number of "organ-specific" autoimmune diseases such as "lupoid" chronic active hepatitis, type I diabetes mellitus, myasthenia gravis and thyrotoxicosis that are associated with the production of autoantibodies.[21] The finding, therefore, of a greatly increased prevalence of HLA-B8 and HLA-DR3 is suggestive that immunologic factors may be involved in the pathogenesis of PSC. This suggestion has been strengthened by a number of recent studies that have shown humoral and cellular immune abnormalities in PSC.

Humoral Immune Abnormalities

Like primary biliary cirrhosis,[15] a disease with which it shares many features, symptomatic primary sclerosing cholangitis is characterized by hypergammaglobulinemia, often with a disproportionate elevation of serum IgM levels.[2]

Although characteristically absent, smooth muscle antibody and antinuclear factor are found in some patients with PSC.[2] These antibodies are usually present only in a low titer and may simply represent a nonspecific result of parenchymal liver damage. We have recently shown, however, that at least two other specific serum autoantibodies are present in PSC patients with ulcerative colitis.[22,23] In our studies 62.5% of patients with ulcerative colitis and PSC have circulating anticolon antibodies compared with only 17% of patients with ulcerative colitis alone.[22] The anticolon antibody did not cross-react with human liver and was not associated with the presence of the HLA-B8 phenotype.[22] We were also able to demonstrate a separate antibody to portal tracts, probably to proliferating bile ductules, from human obstructed liver in the serum of 53% of patients with PSC and ulcerative colitis.[23] This antibody was present in only one patient with ulcerative colitis alone and, interestingly, was closely associated with the HLA-B8 phenotype.[23] The antibody was not found in the serum specimens of 20 patients with extrahepatic bile duct obstruction or 20 with primary biliary cirrhosis. Studies in organ-specific autoimmune disease such as type I diabetes mellitus and pernicious anemia have shown a correlation between serum cytotoxic activity and surface-reactive but not cytoplasmic autoantibodies.[24,25] Further studies are needed in PSC patients to determine whether the portal tract antibody is cytoplasmic, cytotoxic or both.

Additional evidence for the importance of humoral mechanisms in the development of PSC comes from a study by Bodenheimer and colleagues.[26] These workers found elevated circulating immune-complexlike material by at least one method (of two used in the study) in 16 of 20 patients who had PSC with and without ulcerative colitis compared with controls with and without colitis. Immune complexes have also been found in the bile of PSC patients.[27] However, elevated levels of serum immune complexes are not specific for PSC and are found in cases of various liver diseases.[26] Further studies are needed to characterize the nature of the antigen and antibody components of the complexes, which may simply represent an epiphenomenon. It is possible, however, that antibodies against hepatobiliary antigens, such as we have recently described, may form immune complexes in the liver, which play a direct role in tissue injury.

Cellular Immune Abnormalities

Few studies of the cellular immune system have been carried out in PSC. McFarlane and associates found an inhibition of leucocyte migration in response to biliary antigens in patients with PSC, suggesting that their lymphocytes may react with specific antigens in biliary epithelial cells.[28] Similar changes were observed in cases of primary biliary cirrhosis and chronic active hepatitis but not in other forms of cholestatic liver disease.

Schrumpf and co-workers studied T-cell subsets in 11 patients with ulcerative colitis and PSC.[17] They could not find any abnormality in total T-cell numbers or in the ratio of helper to suppressor cells, compared with normal controls.[17]

It is likely, however, that there will be some abnormality in T-cell function in patients with PSC. It has been shown in patients with dermatitis herpetiformis and in normal controls that the HLA-B8 and -DR3 antigens are associated with a low number of Fc-receptor-bearing T cells and a functionally defective Fc-receptor function.[29]

Relationship With Ulcerative Colitis

On the evidence presented it seems likely that PSC is an immunologically mediated disease. How then to explain the close association with ulcerative colitis?

It has been suggested that immunologically mediated diseases are the result of an interplay between independent, antigen-nonspecific defects and antigen-specific defects.[15] The HLA-B8- and HLA-DR3-linked gene is in some way responsible for an antigen-nonspecific increase in immune responsiveness[21] and the disease specificity in PSC must reside in some other non-HLA-linked, genetic or environmental influence somehow linked to ulcerative colitis. The situation may be analogous to the association of ankylosing spondylitis with ulcerative colitis. Although the prevalence of HLA-B27 is not increased in ulcerative colitis, in patients with ulcerative co-

litis and HLA-B27 there is a higher risk for ankylosing spondylitis developing than in controls.[30] There is evidence of antigenic cross-reactivity between HLA-B27-positive lymphocytes and antigens present on *Klebsiella pneumoniae*.[31] It is postulated that this may result in disease by either the production of microbial antibodies that also have an "antiself" activity or that *Klebsiella* antigens may bind to the HLA complex, rendering it susceptible to immune attack.[30] As previously discussed, approximately one fifth of patients with ulcerative colitis have circulating anticolon antibodies, which are not seen in normal controls.[22] The colonic antigen is probably a mucopolysaccharide located in the cytoplasm.[32] It shares determinants with a heterogenetic antigen that is a constituent of most Enterobacteriaceae strains,[33] including *Escherichia coli* O14, which has been shown to cross-react with the colon antigen.[34] The significance of anticolon antibodies in the pathogenesis of ulcerative colitis is unclear, as they are not directly cytotoxic to human colonic cells in tissue culture.[35] They may act, however, by invoking antibody-dependent cell-mediated cytotoxicity against colonic epithelium in cases of ulcerative colitis.[36] The distinct portal tract antibody in PSC may also represent a cross-reacting antibody to an enteric microorganism. This antibody, in genetically predisposed patients with and without ulcerative colitis with HLA-B8, HLA-DR3 and heightened immune responses, could also play a role in the development of PSC through the variety of direct or indirect immunologic mechanisms already discussed.

Implications for Therapy

Symptomatic PSC is a severe, debilitating disease usually culminating in death from progressive liver failure or bile duct carcinoma.[2,5] Current medical therapy is unsatisfactory.[9] If our hypothesis is correct, then immunosuppressive agents such as corticosteroids or cyclosporine administered either singly or in combination may be beneficial at an early stage. We and others have stated that corticosteroids should not be used in cases of long-standing PSC because of the hazards of corticosteroids accentuating osteoporosis in patients with cholestasis.[2,5,9] There has been no controlled trial, however, and it is possible that patients with early disease may benefit from a regimen of corticosteroids.[37] Cyclosporine is a new immunosuppressive agent that may prove to be of benefit in PSC, although in view of its numerous side effects it should be studied only in a carefully controlled and monitored clinical trial.

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Drownings of Children and Youth in a Desert State

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Despite the fact that New Mexico is a desert state, the drowning rate (4.3) is 40% higher than that nationally (3.0). More than half of those who drown are younger than 25 years, toddlers and adolescents being at greater risk than other age groups. In an epidemiologic study of a six-year period, male drowning victims outnumbered female and American Indian and Hispanic victims outnumbered whites. Other major risk factors were epilepsy, mental retardation and alcohol abuse. In most drownings in the under-25 age group, the victim was involved in recreation near the water or swimming, although many were partially or fully clothed. Most drownings occurred in lakes, ditches or rivers. Because New Mexico is not a water-oriented state, public awareness of drowning hazards needs to be increased and more intensive preventive efforts instituted.

(Davis S, Ledman J, Kilgore J: Drownings of children and youth in a desert state. West J Med 1985 Aug; 143:196-201)

Drowning is a common cause of death in children and youth throughout the world.[1] In the United States it is second only to vehicle accidents as the most common cause of accidental death in persons younger than 25.[2] Most studies of drownings have looked at densely populated, water-oriented regions,[3-8] with the assumption that drowning is not as serious a problem in areas where fewer people participate in water sports and activities. The results of our study show that this assumption may be false.

Unlike Maryland,[8] Florida,[3] Hawaii[4] and Australia,[5-7] neither climate nor geography in New Mexico encourages water sports. This sparsely populated, rural state is arid and mountainous with few lakes and rivers. Irrigation by canals and ditches is common, however, and this water source has been thought to pose a significant threat to children. There have been no water-related catastrophes—that is, accidents in which five or more persons are killed[9]—in recent years, but spring thaw often creates flooding in places that are dry during the rest of the year.

This description of the state would suggest that mortality due to drowning should not be a major problem. However, New Mexico, with a population of 1,122,500 in 1975, had a drowning rate (deaths per year per 100,000 population) of 3.5 compared with the national rate for the same year of 2.5.[10] A systematic study was done to determine the specific patterns of drownings.

Methods

A list of all drownings of persons between 0 and 24 years of age for the years 1975 through 1980 inclusive was selected from records of the New Mexico State Office of the Medical Investigator, the central depository for all records of accidental death. This list was compared with the records of drowning from the New Mexico Health and Environment Department Vital Statistics Bureau. In a few cases, because the two listings were not identical, additional cases were added.

Each original case file was reviewed for pertinent information from the investigator's report and, when available, the autopsy and toxicologic and police reports. Records varied in completeness. Information such as activity before drowning, the body of water, supervision, alcohol consumption and ability to swim was incomplete in some cases.

Information on age, sex and county of death was available in all cases. Ethnicity was specified for American Indians and blacks, but Anglo* and Hispanic were usually grouped together as whites. Hispanic ethnicity was assigned according to the *1980 Census List of Spanish Surnames.*[11] Denominators were obtained using 1980 census figures by individual year of age, sex and ethnic groups.[12,13] Estimates for mid-1977 were obtained by "younging" the population. A detailed explanation of the denominator calculations may be obtained on request from the New Mexico Tumor Registry, 900 Camino de Salud NE, Albuquerque, NM 87131.

Results

Age, Sex and Ethnicity

A total of 329 drownings was reported in New Mexico

*Anglo designates a white inhabitant of the United States of non-Hispanic origin.

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TABLE 1.—*Number of Drownings in New Mexico by Age, Sex and Ethnic Group, 1975 Through 1980*

Age Years	Males					Females					Total
	Anglo	Hispanic	American Indian	Black	All Males	Anglo	Hispanic	American Indian	Black	All Females	
0-4	18	11	4	0	33	12	6	2	0	20	53
5-9	2	4	3	0	9	2	2	0	1	5	14
10-14	6	9	2	2	19	1	7	0	0	8	27
15-19	12	20	12	1	45	1	3	1	0	5	50
20-24	16	18	6	0	40	2	3	2	0	7	47
Total	54	62	27	3	146	18	21	5	1	45	191

All ages = 329

over a six-year period, 1975 through 1980 inclusive. More than half of the deaths, 191 (58%), were of persons younger than 25 years. The highest rate of drowning (8.2 per 100,000 annually) occurred in the 0 to 4 years age group, closely followed by those in the 20 to 24 (6.5) and 15 to 19 (6.4) years age groups. The total number of drownings by sex, age and ethnicity for the six-year period are shown in Table 1.

A disproportionate 76% of the drownings of persons younger than 24 years involved male victims. As both Table 1 and Figure 1 show, male victims outnumbered female victims for all ages.

Rates by sex and ethnicity are given in Figure 2. The highest rates are those for male victims in the following order: American Indians (14.9), Hispanics (8.4) and Anglos (6.5).

Location and Activity Before Drowning

Figure 3 gives the frequency by body of water in which a drowning occurred and by the activity of the victim before the drowning. In New Mexico, most drownings (71%) occurred in lakes, ditches or rivers.

Immediately before their deaths, 74 of the victims were playing, fishing, picnicking or involved in other recreation near but not in the water. Another 55 were reported to be swimming. Many of these victims were found fully or partially dressed, indicating that swimming may not have been a planned activity. Swimming was the most frequent activity before the accident only for lake, pool and pond drownings. In river and ditch drownings, most victims were involved in activities near but not in the water.

There were seven multiple drownings. In each of six cases, two persons died and, in another, three adolescent girls drowned after they fell from a dam into a river and were washed through flood gates. Of the two-person drownings, two involved scuba divers, two were related to acute alcohol abuse and two were rescue attempts.

In addition to the two multiple drownings, there were three single drownings during rescue attempts. There were also several cases in which a rescue was attempted, and the victim, in his or her panic, endangered the rescuer and caused the attempt to be abandoned.

Predisposing Factors

In some drownings important predisposing factors were present and may have contributed to the drowning. For example, 12 victims had a history of seizures or mental retardation (or both), which may have compromised their ability to protect themselves in water. The most common factor that may have compromised victims was the use of alcohol. It was difficult to determine the exact prevalence of alcohol use in association with drowning because blood alcohol determinations were not done routinely. For the most part, blood alcohol concentrations seemed to have been measured when the circumstances surrounding the drowning were suggestive of

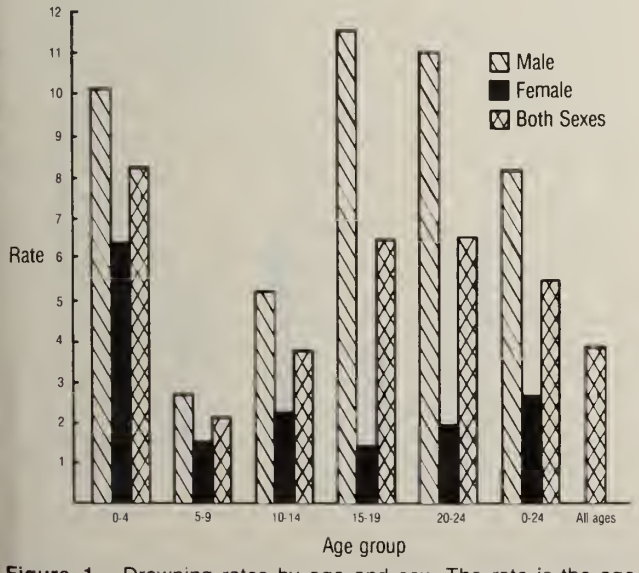


Figure 1.—Drowning rates by age and sex. The rate is the age-adjusted rate per year per 100,000 based on the 1977.5 adjusted census.

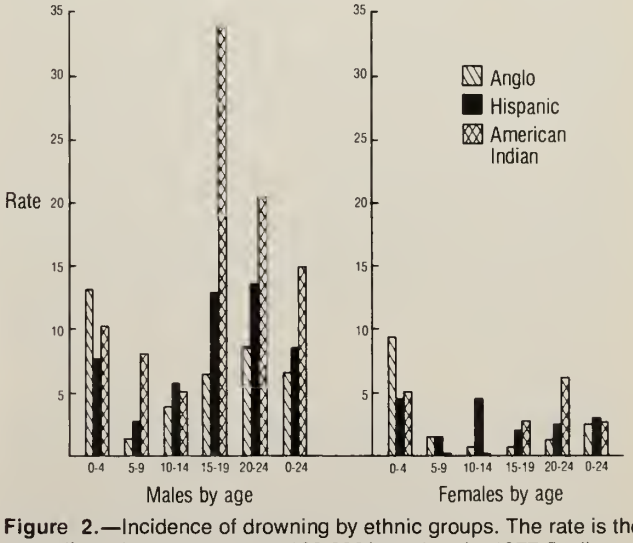


Figure 2.—Incidence of drowning by ethnic groups. The rate is the age-adjusted rate per year per 100,000 based on the 1977.5 adjusted census.

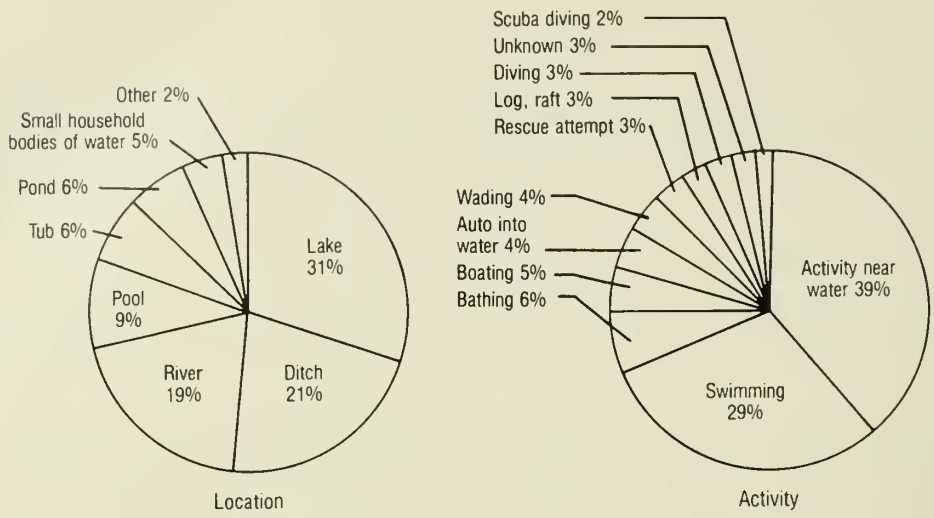


Figure 3.—Frequency of drowning by activity and location.

alcohol use. In several cases in which alcohol determinations were not made, however, eyewitness reports that the victim had been drinking were present in the file. Because all those drownings in which an alcohol level was not determined were assumed not to be alcohol related, the prevalence of alcohol use in relationship to drownings is thought to be underreported.

Of the 191 victims listed by the Office of the Medical Investigator, 90 had alcohol determinations. Of the 43 who had evidence of alcohol use, 25 had an alcohol concentration of greater than 0.1 mg per dl and 18 had a value of 0.01 to 0.1 mg per dl. These 43 cases are classified as alcohol-related drownings. They were compared with those in which alcohol concentrations were not determined plus those in which alcohol determinations gave negative results.

All alcohol-related drownings occurred in persons 15 years or older: 20 were in the 15 to 19 years age range and 23 were in the 20 to 24 years age range. In the 15 to 24 years age group, 44% of all drownings were alcohol related. Only four of the alcohol-related drownings involved female victims.

Rescue and Resuscitation

Of the 91 drownings, resuscitation attempts were recorded in 46 (24%). Six victims were still being resuscitated when they reached the hospital. Five lived from a few minutes to a few days, and one person survived in a coma for 4½ months. It is noteworthy that 13 of the 46 resuscitation attempts occurred at swimming pools. This represents 13 of 18 of the pool drownings. Only 9 of 97 drownings in lakes, reservoirs and rivers resulted in resuscitation attempts. In 4 of 9 bathtub drownings, 3 other home drownings, 1 car submersion and 15 other drownings in small bodies of water, resuscitation was attempted. No data on successful resuscitations were available.

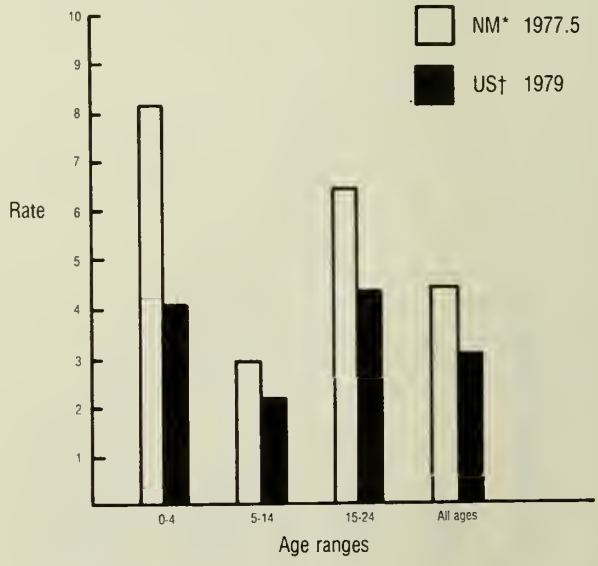
Discussion

There may be a false assumption that drowning is a problem only in water-oriented regions. The New Mexico drowning rate for all ages was 4.3, calculated for the midpoint between 1975 and 1980, whereas the rate for the whole United States was 3.0 for 1979.[2] Figure 4 shows that drowning rates in New Mexico were higher than national figures for toddlers, children and adolescents/young adults as well.

Other states that report a high incidence of drowning such as Florida,[3] Hawaii[4] and Maryland[8] are characterized by the universal presence of bodies of water and may have climates that allow water-related activities to be pursued year round. In contrast, the climate of most of New Mexico is warm only in the summer and there are fewer than 20 lakes with state recreational facilities in a state of more than 77,866,240 acres.[14] Because this is not an environment that fosters water sports to any major degree, other factors contributing to the substantial loss of life due to drowning should be considered.

Human Factors

Sex, age and ethnicity. We found that the distribution of drownings by sex and age was similar to that in other studies and that reported in national and international statis-



*Age-adjusted rate per year per 100,000 based on the 1977.5 adjusted census.
†Figures from National Safety Council.[2]

Figure 4.—Comparison of drowning rates for New Mexico and for the United States.

tics.[1-5,7,8,15-17] Drowning victims of all ages are more likely to be male than female.[3-5,15-17] This may be due to the greater level of exploration and risk taking exhibited by and encouraged in men and boys. In addition, male children may be less closely supervised than female children.[17] Another familiar pattern is the age distribution of the victims. Toddlers[1,2,4,7,15] and adolescents[2,8,15] are at greater risk than children in other age groups.

A third human factor in the New Mexico study was ethnicity. Although no other studies have specifically looked at drowning rates of Hispanics and American Indians, it is known that the overall accident rate for these groups is high.[18-21] Other studies have shown similar high rates for minority populations.[3,8] Socioeconomic and cultural factors obviously play an important role in the cause of accidents such as drowning.

Activity before drowning. Another important human factor is the activity of the victim before drowning. Nationwide, swimming and playing near water are the activities that pose the greatest threats for children and young people aged 0 to 24 years.[15-22] Of the two activities, the New Mexico study found recreation near the water (39%) more common before drowning than swimming (29%).

One study reports that nationally water sports other than swimming (including boating, rafting, skin and scuba diving) accounted for 13% of 3,303 drownings in the 0 to 24 years age group. In all, 7% of the total drownings in this age group were boating accidents.[15] In New Mexico 13% of the drownings in the 0 to 24 years age group were also attributed to water activities other than swimming or wading. Only 10 (5%) were accidents involving boats. One victim was a 3-year-old girl who disappeared from a houseboat. The other nine were all males and ranged in age from 12 to 24 years. Seven were fishing or boating in small boats on lakes or rivers when the boat was overturned or they fell into the water. Five of the seven either were reportedly drinking or had significant blood alcohol concentrations. None wore life jackets. Five other deaths occurred after falling from a raft, kayak or canoe. One of these five victims had a significant alcohol level. One, who was kayaking in river rapids, wore a life jacket. In addition, a 13-year-old boy on an inner tube and another 13-year-old boy on a log were nonswimmers who slipped from their makeshift device into the water and drowned. Four deaths (involving two pairs of divers) were reported among scuba divers. There were no deaths of water skiers. Most of these drownings are characterized by preventable human factors.

Multiple drownings and rescue attempts. Many drowning accidents are prevented by other people who are present and can assist the victim. However, occasionally multiple drownings occur either because neither person can handle the water conditions or because a person attempting rescue is lured into a dangerous situation. The *Statistical Bulletin of the Metropolitan Insurance Companies* reported 143/4,962 (3%) drowning deaths occurred during rescue attempts.[15] In the five-state study reported by Press and co-workers, 42/1,024 (4%) drownings occurred in persons who were trying to save someone else.[22] In the New Mexico data, 5/191 (3%) of the deaths were clearly associated with rescues. Rescue attempts, though not recorded as such, could have been a factor in several other multiple drownings.

There is little information on multiple drownings other than the association with rescue attempts. In one study multiple drownings were reported in skin and scuba divers but the occurrence was in only 5% of the total diver drownings.[23]

Predisposing factors. We and others[8,24,25] have identified a small group of victims with disabling conditions that may have contributed to their drowning. In our study, 12 victims had predisposing disabling factors other than alcohol consumption. Eleven had a seizure history, mental retardation or both. Five of these died in bathtubs. Another victim had a history of drug abuse and had head trauma a week before the accident.

Alcohol use is a known risk factor for injuries.[26,27] Several previous studies have specifically linked alcohol use with drowning.[8,28-30] Mackie[31] reviewed this literature and reported the alcohol-related drowning incidence to be from 14% to 79% of all drownings for various populations.

It is not surprising to find alcohol as a major risk factor in drownings in New Mexico. A recent study by the National Institute of Alcohol Abuse and Alcoholism found New Mexico to lead the country in the number of chronic health problems and number of casualties attributed to alcohol abuse.[32] Our study confirms a high incidence of alcohol-related drownings (44%) in the 14 to 24 years age group. Male victims predominate and there are differences in the incidence of alcohol-related drownings by ethnicity for both sexes.

In general, a high alcohol abuse rate in New Mexico adolescent and young adult populations appears to be a major factor for the excessive drowning rate in the state.

Environmental Factors

Lakes, rivers and ditches. As expected, the incidence of drowning by body of water varies widely depending on the availability of water sources in different areas.[22] In data compiled for all ages from the whole United States, most drownings occurred in lakes (23%), rivers (22%), swimming pools (13%) and salt water sources (9%).[33] In Florida most drownings occur in swimming pools followed by canals and then lakes or ponds,[3] whereas in Maryland drownings are most frequent in rivers, then lakes and then salt water sites.[8] In Honolulu the rank order of drowning sites is swimming pools, salt water sources and domestic bathtubs.[4]

The New Mexico data reflect the pattern of water site availability unique to this area. In the 0 to 24 years age range, most drownings occurred in lakes (31%), followed by irrigation ditches and canals (21%) and then rivers (19%). However, the age of the victim is an important factor in evaluating location of drowning. In the adolescent and young adult groups, 44% and 47%, respectively, died in lakes and 18% and 28% in rivers. In contrast, toddlers were most likely to drown in ditches (38%) or small bodies of water in or around the home (17%) and relatively few died in lakes (9%) or rivers (11%).

Swimming pools. Nationally, swimming pool drownings have increased in recent years, with more pool drownings occurring in Arizona, California, Hawaii and Nevada than in other areas of the country.[34] In New Mexico only 9% of the drownings occur in swimming pools. This is not surprising since there are few private or public pools in the state due to economics and the climate factors mentioned earlier.

Bathtub drownings and other household water sources. Bathtubs have previously been identified as an important site of infant drowning. Unlike other childhood accidents that show a male predominance, the sexes are equally affected in this case. Although most of these incidents involve infants, there is an occasional report of bathtub drowning in older persons with certain predisposing factors.[7,35,36]

In our study, 11 bathtub drownings fell into two categories. Five children younger than 25 months drowned after being left unattended in a bathtub. Six older children or young adults with predisposing disabling conditions such as seizures or mental retardation died in tubs. All but one of the bathtub drowning victims were female.

Nine other unattended toddlers died in small household bodies of water such as cesspools and stock troughs. Two of these children died in buckets containing only a few inches of water. Pail-immersion accidents have been reported by previous investigators[37-40] as well.

Rescue and resuscitation. The environment affects chances of rescue and resuscitation. Many of the drownings occurred in unsupervised bodies of water characterized by dangerous, steep and muddy banks; swift currents; cold temperatures; drop-offs, and murky water filled with debris—all factors making swimming unsafe and prompt rescue difficult or impossible.

If a victim was recovered quickly or if time submerged was unknown, resuscitation was usually begun at the scene and continued in transport by emergency personnel. The resuscitation attempt rate (24%) was low, reflecting the many victims who were not recovered immediately.

Of the 18 persons who died in swimming pools, 13 (72%) resuscitation attempts were recorded. Lifeguards were involved at only three sites, however. In addition, it is known that resuscitation was attempted in 5 of 11 bathtub drownings and in 3 other home drownings. In one case two persons drowned after their car left the road and plunged into water. They were easily found and resuscitation was attempted. Fifteen others who received resuscitation drowned in smaller bodies of water such as ditches, ponds or stock tanks. Thus, only 9 of the 46 victims in whom resuscitation was attempted were recovered from large bodies of water such as lakes, reservoirs and rivers. The resuscitation attempt rate at these sites was 9 in 97 (10%). As expected, the chance of a resuscitation attempt varied with the drowning site and seemed to be related to rapidity with which the victim could be found and recovered.

Summary

Distribution of immersion accidents by body of water in New Mexico varies from that described in different geographic areas.[3-5,8,22] The greatest number occurred in lakes, ditches and rivers. Almost as many drownings happened in bathtubs, ponds and small household bodies of water as occurred in swimming pools, each accounting for less than 10% of the total. Recreation near water and swimming were the most common activities before drowning. It is of interest to note, however, that victims were often fully or partially clothed, in some cases even wearing boots. This suggests that swimming may have been a spontaneous rather than a planned activity. In most cases, the location of drowning was not a supervised recreational area. The population is generally unaware of possible hazards and uneducated regarding aquatic sports and safety. It is ironic that New Mexico's lack of water may actually contribute to the high incidence of drownings.

While the distribution of drownings by body of water may be geographically specific,[22] the population groups at risk appear to be universal. Males,[1,3-5,15-17] toddlers,[1,2,4,7,15] adolescents[2,8,15] and minorities[3,8] appear more likely to drown no matter where the accident occurs. Similar factors predisposing to drowning such as epilepsy,[8,24,25] mental retardation[23,24] or alcohol abuse[8,26-31] have been reported in other studies.

Of the many factors that contribute to the cause of drowning, the role of human behavior appears most prominent. Socioeconomic and cultural factors reflected in the differences in death rates by ethnicity must also be taken into consideration. While it is not likely that a drowning prevention program could make many changes in social, political and economic environments, it is conceivable that changes can be made in human behavior and to some extent the physical environment. Efforts should be concentrated in these areas.

The first step should be a statewide media campaign to elevate public awareness regarding the hazards associated with drownings and the particular vulnerability of specific population groups. Particularly dangerous locations need to be publicized. Needed behavioral and environmental changes should be identified and preventive efforts in that direction reinforced. Committing public funds for barrier construction, supervised swimming areas, aquatic education and cardiopulmonary resuscitation should be encouraged. Coordinated efforts of public health, education, community recreation groups and the Red Cross should be visibly supported by publicly documenting their efforts.

Aquatic education should be included in every school program. Communities should join with the schools in combined recreational efforts that teach swimming, water safety and cardiopulmonary resuscitation. In one isolated rural area, children are bused during the summer to a larger community with a pool where they receive instruction in swimming and water safety. Similar efforts should be made in other areas where established programs are not available. Safety instruction should include the dangers of combining alcohol use and swimming and the hazards of swimming in unsupervised bodies of water. Physicians should not overlook the importance of one-to-one safety counseling. Persons should at least have adequate and accurate information with which to make informed decisions.

Drowning epidemiology should be examined by desert states as well as those states that encourage water activities. Data from such epidemiologic studies will focus preventive efforts in the appropriate direction. Without such studies we may overlook important causal factors and misdirect our efforts.

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Blood and Plasma Substitutes—Plasma Expansion and Oxygen Transport Properties

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Because of the risks and costs of blood and blood product infusion, developing blood and plasma substitutes is of significance. Two currently utilized substances, dextran and hydroxyethyl starch, are effective colloid plasma expanders. The dextrans have properties that improve microcirculatory blood flow but are associated with several possible adverse effects. Hydroxyethyl starch is a well-tolerated agent that has efficacy similar to albumin but at a lower cost. Two newer substances, perfluorocarbons and stroma-free hemoglobin, are being developed to improve oxygen transport as well as plasma expansion.

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There are increasingly important limitations to the use of blood and plasma in treating cases of hypovolemic shock. Blood and blood products have limited availability, there is increasing concern over infectious and immunologic risks and the costs involved in obtaining, storing, cross matching, processing and dispersing blood and blood products continue to rise. There is, therefore, a clear role for effective blood and plasma substitutes. Not only do these solutions provide a cost-effective alternative to blood products, they also allow conservation of this limited resource for those patients who most need it.

Electrolyte solutions containing sodium (crystalloids) have been shown to be effective but relatively inefficient plasma volume expanders. They are inefficient because, once infused intravascularly, they distribute over the entire extracellular fluid space, only a relatively small portion of which is the plasma volume. Large volumes of crystalloid fluids, therefore, need to be infused to result in effective plasma volume expansion. Colloid fluids contain larger molecules that diffuse relatively slowly across the semipermeable capillary membranes. These fluids are, thus, effective plasma expanders. Following Starling's concepts in 1896 of colloid osmotic pressure as a regulator of the plasma volume, interest arose in developing colloid plasma expanders. The first colloid plasma substitutes were tested around the turn of this century, when gum acacia was used as a volume expander. This substance is a carbohydrate exudate from *Acacia* trees and was used clinically during World War I. It proved to be highly antigenic, however, and anaphylaxis was common following its infusion.[1] Gelatin solutions derived from collagen were also developed in the early 1900s and these too were used clinically during World War I. Gelatin solutions of 3% to 4% are still used clinically in Europe, but have not been used in recent years in the United States for several reasons. The plasma expansion following gelatin infusion is short lived because of rapid urinary excretion. Further, gelatin infusions are antigenic and anaphylaxis may occur, particularly with repeated infusions.[2,3]

In this review we discuss four examples of modern plasma substitutes, the dextrans, hydroxyethyl starch, perfluorochemical emulsions and stroma-free hemoglobin. Each of these is a colloid fluid with the potential for efficient plasma volume expansion. Stroma-free hemoglobin solutions and perfluorochemical emulsions not only expand plasma volume but can transport additional oxygen as well.

Dextran

In 1944 the dextrans were introduced in Scandinavia as plasma volume expanders. Dextrans are polysaccharides produced by the conversion of sucrose into long glucose polymers by the bacterial enzyme dextransucrase. Clinically used dextrans are produced by a specially developed strain of bacterium, *Leuconostoc mesenteroides*. The molecules produced by the bacteria are very large, with molecular weights of several millions. For intravenous infusion, partial acid hydrolysis produces dextran fractions of specified weight ranges. Two dextran solutions are now most widely used, a 6% solution with an average molecular weight of 70,000 (dextran 70) and a 10% solution with an average weight of 40,000 (dextran 40, low-molecular-weight dextran). These

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ABBREVIATIONS USED IN TEXT

2,3-DPG = 2,3-diphosphoglycerate
HES = hydroxyethyl starch
P-50 = oxygen half-saturation pressure of hemoglobin
Pao_2 = partial arterial oxygen pressure (tension)
PFC = perfluorochemical

molecular weights are averages as dextran solutions, in fact, contain a range of various-sized dextran molecules. The dextrans can be efficiently produced in large quantities and stored for many years at room temperature either in powdered form or in solution.

Dextran is mainly excreted unchanged in the urine. The rate of renal excretion depends on molecular size, with smaller dextran molecules being excreted rapidly and larger molecules (above 50,000 molecular weight) excreted very slowly. Dextran molecules not excreted in the urine slowly diffuse into the interstitium where uptake into the reticuloendothelial cells and slow metabolism to carbon dioxide occur.[4] Reticuloendothelial cell dysfunction as a result of this uptake has been postulated, but the clinical implication of this remains unproved.

The plasma half-life of dextran solutions depends on their molecular size (dextran 40 being excreted more rapidly than dextran 70), but dextran 40 solutions have a higher oncotic effect per gram infused and, thus, produce a more pronounced, if more short-lived, plasma volume expansion.[5]

In addition to plasma volume expansion, dextran solutions have several physiologic effects that have clinical import. Dextran solutions have antithrombotic effects, probably mediated by inhibition of platelet aggregation in addition to augmentation of microcirculatory blood flow.[6-8] One of the most important implications of dextran administration to patients in shock is its effect on microcirculatory blood flow. A major pathophysiologic deficit following shock is decreased microcirculatory blood flow, which impairs oxygen transport to the tissues. Administering dextrans, particularly the low-molecular-weight dextrans, may greatly improve microcirculatory flow. This effect is mediated by two mechanisms: (1) the viscosity of blood is decreased by hemodilution, as with any effective volume expander; (2) low-molecular-weight dextrans specifically inhibit erythrocytic aggregation and, thus, reverse and prevent erythrocytic sludging.[4,9]

Anaphylactic reactions to dextran are unusual, occurring in 0.03% to 0.07% of patients, but may be severe and even fatal. When reactions occur, they do so usually during infusion of the first 100 ml. Patients may have severe anaphylactoid reactions even with no previous exposure to dextran given intravenously.[10] Close clinical observation of patients during the initiation of dextran infusion is mandatory.

Dextran, as previously discussed, affects normal coagulation. This effect is dose related—that is, low doses of dextran (less than 1.5 grams per kg of body weight) are not associated with clinical bleeding, but platelet adhesiveness is decreased, and plasma levels of clotting factors are also decreased.[5] Larger doses of dextran have been associated with significant bleeding complications.[11] Precipitation of acute renal failure has been thought to follow infusion of dextran, although this is controversial.[5,12,13] Low-molecular-weight dextran has been particularly implicated. A possible mechanism for this is the accumulation of the dextran molecules in the renal tubules, causing tubular plugging. Renal failure following dextran use is more often reported when renal perfusion is reduced or when preexisting renal damage is present.

Another problem that has been reported with dextran infusion is the subsequent difficulty in cross matching blood for transfusion.[14] This effect may be mediated by the adherence of the dextrans to antigens on the red cell membrane. In practice, this problem can be circumvented by obtaining a blood specimen for cross matching before infusion.

Dextran was initially used clinically during the Korean War. Since that time there have been numerous experiences with more than 60 million units of dextran infused into patients.[5] Problems have been delineated, particularly the risk of increased bleeding and anaphylaxis. The current uses of dextrans as plasma expanders fall into several categories.

Dextrans are effective plasma volume expanders with efficacy equal to or superior to albumin. A number of studies have shown this plasma volume expansion, with subsequent hemodynamic improvement.[5,15-18] A practical restriction of dextran in this regard, however, is its effect on clotting, necessitating dose limitation in bleeding and perioperative patients to 1,000 to 1,500 ml per 24 hours. Furthermore, the possibility of precipitating acute renal failure has limited its use in oliguric patients. Finally, the possible impairment of blood cross matching must be considered in this setting.

Low-molecular-weight dextran has also been used effectively as a plasma substitute for priming in extracorporeal circulation. In some studies it has been found to have advantages over other colloid solutions for this purpose, in decreasing erythrocyte and platelet destruction.[19,20]

The improved microcirculation following low-molecular-weight dextran infusion may offer therapeutic advantage in reversing erythrocytic sludging following severe trauma, shock and sepsis.[5,9,15,21,22] Dextrans have also been studied and used as possible effective modalities in treating patients with myocardial ischemia, cerebral ischemia and peripheral vascular disease and in maintaining vascular graft patency.

Hydroxyethyl Starch

Starch is the energy storage polysaccharide of plants and is analogous functionally and structurally to glycogen, the energy storage polysaccharide molecule of animals. Starch is composed of two types of glucose polymers: amylose, a linear molecule, and amylopectin, a highly branched molecule that structurally resembles glycogen. Amylopectin is well tolerated when infused intravascularly into animals, but is rapidly hydrolyzed enzymatically (amylase hydrolysis), with a half-life of only about 20 minutes. In the early 1960s, work by Thompson and others showed that modification of the amylopectin molecule would make it more stable within the plasma.[23] This was successfully accomplished by substituting hydroxyethyl groups to create hydroxyethyl starch (HES).

Commercially available HES solutions contain a heterogeneous solution of HES molecules, with an average molecular weight of 69,000, similar to albumin. The range of molecular size, however, is from 10,000 to 100,000. This has implications when considering elimination of HES from the vascular space. Smaller molecules are excreted unchanged into the urine, whereas larger molecules slowly diffuse into the interstitium where slow enzymatic degradation occurs. In normal subjects, HES is nearly completely cleared from the

plasma within two days (half-life is 17 hours), yet only about 50% of the HES is eliminated from the body. The remaining HES is eliminated very slowly and much of the initial dose persists for weeks after infusion, some of the larger HES molecules probably accumulating in the reticuloendothelial cells.[24]

Hydroxyethyl starch appears to be an extremely well-tolerated plasma expander, with adverse effects infrequent and relatively mild. Allergic reactions to HES are distinctly uncommon; unlike dextran, HES is not antigenic.[23] In one large study, the incidence of allergic reactions to HES was 0.085% compared with 0.011% for albumin infusion.[25] In this large study there were no fatal anaphylactic reactions to HES.

The only clinically important adverse effect of HES infusion appears to be some impairment of coagulation. This effect seems to be dose related. Low doses have no effect on coagulation, whereas moderate doses (20 ml per kg) have the following effects: platelet counts may transiently decrease or remain normal; platelet function, including platelet adhesiveness, remains intact and bleeding times remain normal; prothrombin time and partial thromboplastin time may be prolonged, and fibrinogen levels may decrease.[23,26,27] Although these effects may be measured, there is no evidence of clinical bleeding problems with HES infusions of as much as 20 ml per kg.[28] There have been no controlled human studies of larger infusions with HES, but studies of animals have shown increased incisional bleeding, increased intraoperative blood loss and spontaneous serosal bleeding when very large doses of HES are infused.[11]

A problem of unclear significance with HES infusion is an occasional elevation of the serum amylase level. Whether this hyperamylasemia is the result of subclinical pancreatitis, whether HES acts as a physiologic stimulant to pancreatic amylase secretion or whether it is the result of amylase aggregation is unknown.[29] The only important clinical implication appears to be that HES infusion in patients with pancreatitis might compromise the interpretation of serum amylase values. Unlike dextrans, HES does not interfere with the typing or cross matching of blood, and there appears to be no adverse effect on renal function.[23]

Hydroxyethyl starch has been well studied for its efficacy as a plasma volume expander. HES (6% solution in saline) increases plasma volume from 71% to 230% of the volume infused.[30-34] The colloid osmotic pressure is increased significantly following HES infusion, and this explains the ability of HES to expand the plasma volume by more than the infused volume. The colloid osmotic pressure remains elevated two to five days following HES infusion, corresponding to the plasma half-life of HES.

As would be predicted from its efficacy as a plasma volume expander, HES infusion has good hemodynamic effect. In comparative studies of fluid therapy patients, infusing 6% HES solutions has increased central venous pressure, pulmonary capillary wedge pressure, cardiac output and ventricular stroke work, with efficacy equivalent to that of 5% albumin infusion.[28,35,36] There have been no reported bleeding problems in these studies, even in perioperative patients. HES has also been successfully used as a priming solution for cardiopulmonary bypass. Although a comparative study showed that postbypass platelet counts were lower following HES compared with albumin prime, no difference occurred in chest tube drainage, blood use, hemoglobin or fibrinogen levels or coagulation times.[37]

In comparison with dextran, HES has similarities and differences. Both dextran and HES effectively raise colloid osmotic pressure and plasma volume, though the plasma volume increase may be greater and somewhat more sustained following infusion of higher molecular weight dextrans. Dextrans are more useful agents in decreasing blood viscosity and increasing microcirculatory blood flow, and thus have advantage as antithrombotic agents and as therapy for microcirculatory flow disturbances. HES, on the other hand, appears to be associated with fewer adverse effects, including a lower incidence of anaphylaxis, fewer bleeding problems and no adverse renal effects. Current 1985 costs to our hospital for 500 ml of 6% HES is about $40 compared with $27 for dextran 40 and $106 for 5% albumin.

Perfluorochemicals

Perfluorochemicals (PFCs) are 8 to 10 carbon fluorinated hydrocarbons. Oxygen is highly soluble in liquid PFC, and this inspired the concept that these substances might prove useful as "artificial blood."[38] However, PFCs are immiscible in aqueous solutions, including plasma. Thus, its potential use as a blood substitute has been delayed by the necessity of suspending PFC in an emulsion suitable for intravascular infusion.

In 1968, total exchange transfusions in animals were successfully done using such a PFC emulsion.[39] There were, however, significant problems with these early emulsions, including prolonged tissue retention times and pulmonary and hepatic toxicity.[40] During the 1970s, Japanese workers developed an improved emulsion, named "Fluosol-DA 20%" (Fluosol).[41] This emulsion is 20% PFC by weight and uses two PFC molecules, perfluorodecalin and perfluorotripropylamine. Poloxamer 188 (Pluronic F-68) and egg yolk phospholipid are emulsifying agents, and hydroxyethyl starch is added to increase oncotic pressure. Fluosol must be stored frozen and infused within 24 hours after thawing.

Perfluorochemical emulsions are eliminated unchanged through the airways. The particle size of the Fluosol-DA emulsion is quite small, with a mean diameter of 0.1 micron, which contributes to elimination through the alveolar membrane. (There are other advantages to this small emulsion particle size, as will be discussed.) There is also some uptake of PFC emulsions by the reticuloendothelial cells. The plasma half-life of Fluosol is about 17 hours after infusion of 20 ml per kg.[42,43]

Because oxygen is dissolved in PFC emulsions, not bound as it is to hemoglobin, the amount of oxygen transported depends on the partial pressure of oxygen in the arterial blood (Pa_{O_2}). Although PFCs have about 20 times the solubility for oxygen as plasma, significant volumes of oxygen are still only dissolved at high Pa_{O_2} values. Thus the clinical use of PFC emulsions requires good pulmonary function and high inspired oxygen concentrations. An advantage of this relatively low "affinity" of PFC for oxygen is that nearly all oxygen dissolved in PFC at arterial oxygen tensions will be released to peripheral tissues at tissue oxygen tensions.

Plasma volume expansion is an important aspect of why PFC emulsions improve oxygen transport. Beyond simple

preload increase, however, the PFC emulsions may improve peripheral blood flow by improved microcirculatory flow. The small PFC emulsion particles (1/70th the size of erythrocytes) may flow through constricted areas of the microcirculation not accessible to erythrocytes. This may improve peripheral tissue oxygenation both by delivering oxygen dissolved in the PFC and by increasing plasma flow and delivery of that oxygen dissolved in plasma.

Fluosol was given to normal volunteers and tested in clinical trials in Japan in 1978.[44,45] It was first used in the United States in 1979, and limited clinical trials have since been undertaken, largely in anemic and bleeding patients who refused blood on religious grounds. There are limited published physiologic data on the efficacy of Fluosol infusion in terms of plasma expansion and oxygen transport. Mitsuno and coworkers reported that Fluosol infusion did result in significant plasma volume expansion.[46] Tremper and colleagues and Waxman and associates reported small series of anemic patients who had some improvement in oxygen delivery and oxygen consumption following Fluosol administration.[47,48]

A number of adverse effects have been possibly related to administering PFC emulsion. These include transient leukopenia, elevated liver function test values, increased pulmonary arterial pressures, transient hypotension and pulmonary failure.[48-50] It appears likely that an emulsifying agent in Fluosol, poloxamer 188, may be responsible for some of these adverse effects.[51]

The clinical usefulness of currently available PFC emulsions as a blood substitute has thus not been well established. A number of limitations of these solutions appear to be problems. First, the volumes of PFC emulsion that have been infused have been quite limited, and with these volumes only a relatively small amount of oxygen can be dissolved. (Even these small amounts might be important, however, in a critically anemic patient.) Second, the plasma half-life is relatively short. Third, in order for Fluosol to dissolve significant volumes of oxygen, very high Pao_2 tensions must be achieved and, therefore, adequate pulmonary function and high inspired oxygen concentrations are necessary. Finally, a number of possible adverse effects following Fluosol administration have been reported; the incidence and clinical significance of these require further investigation.

Further work on PFC emulsions is ongoing and improved emulsions have already been described.[52] It is possible that at least some of the current limitations may be overcome and that PFC emulsions may prove to be extremely useful blood substitutes.

Interestingly, other possible clinical uses for PFC emulsions may have equal or greater promise. These include its use in cases of ischemic heart disease, cerebrovascular disease, peripheral vascular disease, wound healing, microsurgery and cancer therapy.

Stroma-Free Hemoglobin

For almost 70 years now, experimental work has been ongoing in an attempt to develop hemoglobin solutions as oxygen-carrying blood substitutes.[53-58] Human hemoglobin solutions offer a number of theoretical advantages, including the potential to develop a stable, oxygen-binding, colloid volume expander with no antigenicity. The development of clinically usable solutions, however, has been slow. The initial problem with hemoglobin solutions was renal toxicity; this has now been shown to be primarily due to the erythrocytic stromal components of the early hemoglobin preparations, not the hemoglobin itself.[59,60] This has led to the development of stroma-free hemoglobin solutions, which are highly purified hemoglobin solutions, with erythrocytic membrane fragments removed.

Problems with preparing purified stroma-free hemoglobin solutions have been carefully studied.[61] Currently utilized solutions are generally made from the hemolysis of washed, outdated, banked, human packed erythrocytes. This hemolysate is then sequentially crystallized and washed until pure crystalline hemoglobin is produced.[62,63] This protein may be stored in dry form or it may be reconstituted into a solution. While these preparations are relatively stable, there is a gradual breakdown to methemoglobin when they are stored at room temperature; shelf-life is greatly prolonged if stroma-free hemoglobin is stored frozen.[64]

A major possible advantage of stroma-free hemoglobin over other plasma expanders is the ability of hemoglobin to bind oxygen. A major problem, however, exists with the usual stroma-free hemoglobin preparations, increased affinity for oxygen compared with that for erythrocytes.[65] The oxygen half-saturation pressure (P-50) of stroma-free hemoglobin solutions varies from 12 to 16 torr compared with a value of 26 to 27 torr for fresh blood. This increased oxygen affinity (left-shifted oxygen-dissociation curve) is due to the loss of tetrameric hemoglobin, the lack of 2,3-diphosphoglycerate (2,3-DPG) and a higher pH compared with the intracellular erythrocyte pH. The increased affinity for oxygen by stroma-free hemoglobin solutions could lead to inadequate release of oxygen to the tissues, even in the face of adequate circulating volumes of oxygen. While this problem, indeed, is confirmed experimentally, still, in experimental models of shock, stroma-free hemoglobin solutions improve tissue oxygenation when compared with non-oxygen-carrying resuscitation fluids.[55,66,67]

Another major problem with stroma-free hemoglobin solutions is their rapid clearance from the vascular space due to renal excretion and reticuloendothelial cell uptake.[59-70] In experimental studies, stroma-free hemoglobin solutions have a plasma half-life of two to four hours. The rapid loss of hemoglobin molecules creates a further problem, as the effect is that of an osmotic diuretic and can result in intravascular volume depletion. To counteract these effects, a number of hemoglobin complexes have been described that result in a larger species with longer intravascular half-life. A disadvantage of most of these techniques, however, is that they tend to further lower the P-50. Most recently a complex of hemoglobin with pyridoxal-5′-phosphate has been described that reportedly increases both plasma half-life and P-50.[71] Stroma-free hemoglobin has also been encapsulated in artificially produced liposomes, simulating the erythrocytic membrane and allowing the addition of 2,3-DPG.[72] These "artificial erythrocytes" reportedly have normal oxygen-hemoglobin dissociation properties.

Although hemoglobin solutions have been used clinically in various parts of the world, there has been no clinical work evaluating plasma volume expansion and oxygen transport using the most recently developed stroma-free hemoglobin

preparations. Clearly, these solutions offer great potential advantage over other plasma expanders and blood substitutes and continued experimental work and the initiation of clinical trials are of major clinical interest.

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Specialty Conference

Neurobiologic and Psychobiologic Mechanisms in Gastric Function and Ulceration

Moderator
HERBERT WEINER, MD

Discussants
DONALD NOVIN, PhD; CARLOS V. GRIJALVA, PhD; YVETTE TACHÉ, PhD, *and* THOMAS GARRICK, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Associate Professor of Medicine.

The initiation and termination of feeding behavior are not fully understood. The stomach has been implicated as one source of signals regulating food intake. The sight and smell of food are potent stimuli to gastric acid secretion and contraction. The mouth, upper gastrointestinal tract and liver contain receptors regulating food intake; afferent information passes into the brain stem and into the brain areas. Lateral hypothalamic lesions abolish feeding, raise the body temperature and basal gastric acid secretion and produce gastric erosions. Vagotomy and administering propantheline bromide abolish the increased acid secretion after such lesions; they also alter the mucosal barrier permitting diffusion of protons into mucosal cells. Several of the neuropeptides via the central nervous system stimulate or inhibit gastric acid secretion through modulation of the autonomic nervous system. Most animal models of gastric erosions are associated with a reduced body temperature. Unknown is whether or not this association is the result of increased levels of thyrotropin-releasing hormone—a potent stimulus to gastric acid secretion and erosion formation when injected intracisternally.

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The Experimental Production of Gastric Erosion and Its Relation to Human Ulcer Disease

HERBERT WEINER, MD:* Our understanding of the cause and pathogenesis of a disease has often been furthered by the development and use of animal models. However, the pathogenetic mechanisms, anatomic site and nature of the lesion, pathophysiology and course of the disease produced in animal models do not mimic peptic ulcer disease in humans.

With rare exceptions,[1,2] experimental erosions produced in animals are located in either the gastric rumen[3] or fundus[4] and not in the duodenum. Until recently, it was believed that social, behavioral and psychologic factors played a negligible role in human gastric ulcer disease; its pathogenesis was mainly associated with atrophy or a decline in mucosal resistance, or both. Emulsifying agents[5] or drugs, such as indomethacin and salicylates, which inhibit prostaglandin synthesis, are also associated with gastric ulcers in humans and with gastric erosions in animals.[6]

Gastric erosions have also been experimentally produced in animals by many drugs such as histamine and pentagastrin, which increase gastric acid secretion, by starvation,[7] ligating the pylorus and bleeding of the animals.[8,9] Many behavioral techniques produce gastric ulcers: aversive stimulation,[10] conditioning techniques and immobilizing by restraint,[11,12]

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ABBREVIATIONS USED IN TEXT

CCK8 = cholecystokinin 8
CGRP = calcitonin gene-related peptide
CNS = central nervous system
CRF = corticotropin-releasing factor
ODT8-SS = des-$AA^{1,2,4,5,12,13}$ [D-Trp^{8}] somatostatin
TRH = thyrotropin-releasing hormone

with or without cooling the animal.[13] Feeding a rat only once a day enhances its motor activity and in four to five days leads to weight loss, hypothermia and gastric ulceration.[14]

The ultimate aim in such studies is to determine the brain mechanisms that mediate the effects of behavioral interventions and result in altering the physiology of the stomach in such a manner that ulcers ensue. Lesions of the hypothalamus, particularly of the ventrolateral nucleus,[15] and of the hippocampus[16] have been shown to predispose to formation of a gastric ulcer. In animals, the effects of hippocampal lesions can be modified by concurrent stimulation of the medial forebrain bundle.[17] But as Dr Grijalva's discussion shows (see page 212), lateral hypothalamic lesions may produce gastric erosions by mechanisms that differ from those set into motion by other techniques, such as stimulating basal acid secretion and raising the body temperature.

The role of a fall in ambient and core body temperature seems to be critical in the production of many other forms of experimental gastric erosions.[18] Cooling animals enhances restraint-induced gastric erosions. A fall in body temperature probably mediates the effects of premature separation, nutritional and sleep deprivation and enhanced motor activity—all known to produce gastric erosions.

Gastric acid secretion is inversely related to ambient temperature,[19] even though core body and stomach temperatures remain unchanged.[18] At low ambient temperature the acid secretory response to insulin[19] and the release of pepsin are augmented, whereas mucus production decreases.[20] Lowering the core body temperature augments the acid output to histamine administration.[21] Increasing the vagal efferent discharge also increases gastric contractions and compresses the mucosa.

Rats prematurely separated at 15 days from their mothers are at particular risk for restraint-induced gastric erosions.[12] During restraint they cannot maintain body temperature. When these rats are maintained at an ambient temperature of 10°C, their acid output is no greater than normally weaned rats.[18] Therefore, it is not likely that gastric erosions in a prematurely separated rat are the product merely of an enhanced acid output. Other factors may likely play a role: a diminished mucosal resistance, a disruption of the normal ontogeny of acetyl choline, histamine or gastrin receptors or longer lasting and more powerful contractions of the stomach wall. These data suggest that the pathogenetic mechanisms for gastric erosions in rats have not been elucidated and that no single mechanism, or invariant set of mechanisms, is responsible for all forms. In fact, pathogenetic heterogeneity may be the rule.

In humans, gastric ulceration may occur after blood loss (as in rats) and burns, during which the core body temperature also falls. Prostaglandin inhibitors are also associated with gastric ulcers. Recently, two sets of data suggest that gastric ulcer disease in humans is associated with antecedent life changes, albeit not with the degree as that of peptic duodenal ulcer disease. Peters and Richardson reported that the onset of gastric ulcer disease was associated with dramatic events in the lives of two patients.[22] During the height of their symptoms, both basal and maximal stimulated acid output increased; with resolution of their personal problems, acid output fell and the symptoms of the disease disappeared.

Gastric ulcer disease in humans may not be one but several diseases, each with a different pathogenesis, as is the case with peptic duodenal ulcer disease.[23] This conclusion is supported by data from studies of gastric erosions in animal models that may recently have acquired more relevance for gastric (but not duodenal) ulceration in humans.

The Nature and Integration of Signals Controlling Food Intake

DONALD NOVIN, PHD:* Body weight in mature organisms results from a balance of energy intake and output. When intake exceeds output, the excess is conserved as fat deposits in the body. When the opposite occurs and output exceeds intake, nutrient stores (primarily fat) supply the energy substrates not available from exogenous sources—that is, food.

Why is it that for most people the difference between input and output integrated over some reasonable period of time (days or weeks) is equal to zero? And, why is it not for a significant number of other persons? These are difficult questions to answer. Consequently, feeding-related disorders, such as obesity and anorexia nervosa, are difficult to treat.

Energy intake should influence body weight. Other things being equal, the more calories one consumes, the more one will weigh; this is not a linear function, as increased caloric intake substantially increases heat loss, the so-called thermic effect of food.[24] The relative lack of this thermic effect in an obese person may contribute to that condition[25]—a controversial hypothesis.

That body fatness (or some correlate thereof) modifies food intake[26] has been shown experimentally in animals where the first meal after weight loss induced by starvation is larger than any previous spontaneous meal. Conversely, when animals have been fattened in various ways, spontaneous meals are considerably decreased in size.[27] Something about a change in weight (body fatness) alters the strength of signals for hunger and satiety. Because body weight or fatness, or both, fluctuate little with single meals, this variable operates on feeding through a biasing mechanism making other hunger and satiety signals more or less efficacious.

To understand feeding and weight disorders, we must know something of what these hunger and satiety cues might be (short-term control) and how long-term mechanisms (such as body fatness) affect them. Unfortunately, although progress has been made, we are far from a general theory of hunger and satiety.

Historical Perspective

There are three periods in the history of the science of feeding.

Gastric hypothesis. The first systematic theory of feeding was developed by Cannon[28] during the early 1900s and stated that feeding was stimulated by hunger pangs resulting from large stomach contractions and that satiety occurred as a func-

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tion of a quiescent stomach. It was supported by common sense and by some empirical evidence (Figure 1). Its decline as a leading theory occurred for various reasons. Stomach denervation and even gastrectomy, which had slight and transient effects on feeding, were some of the observations inconsistent with the theory.

Dual-center glucostatic hypothesis. Manipulation of the alimentary canal and its innervation yielded slight and transient effects, whereas stereotaxic surgery yielded great and seemingly permanent effects on feeding. This led to the second phase, beginning in the 1940s. Two areas of the hypothalamus were singled out on the basis of results of discrete lesion and electrical stimulation experiments made possible by the new technique; the lateral hypothalamic area became a center identified with hunger and the ventromedial nucleus of the hypothalamus with satiety. This concept, combined with the notion that the major signal was glucose use sensed by the ventromedial nucleus of the hypothalamus, became a powerful and stimulating theory of feeding (Figure 2).

The theory suffered because the notion of "centers" in the brain is misleading. Brain areas do not operate in isolation but as part of widely interconnected systems. It also became clear that there is considerable redundancy in the system. Thus, even after extensive hypothalamic destruction, feeding control is largely maintained.[29] No one organ or signal seems to be necessary for reasonable regulation to continue. For example, although regulation may occur in the absence of the stomach or its innervation, it is misleading to conclude that the stomach does not play an important role under normal circumstances. A simple dual-center system primarily responding to glucose metabolism did not fit enough of the experimental observations.

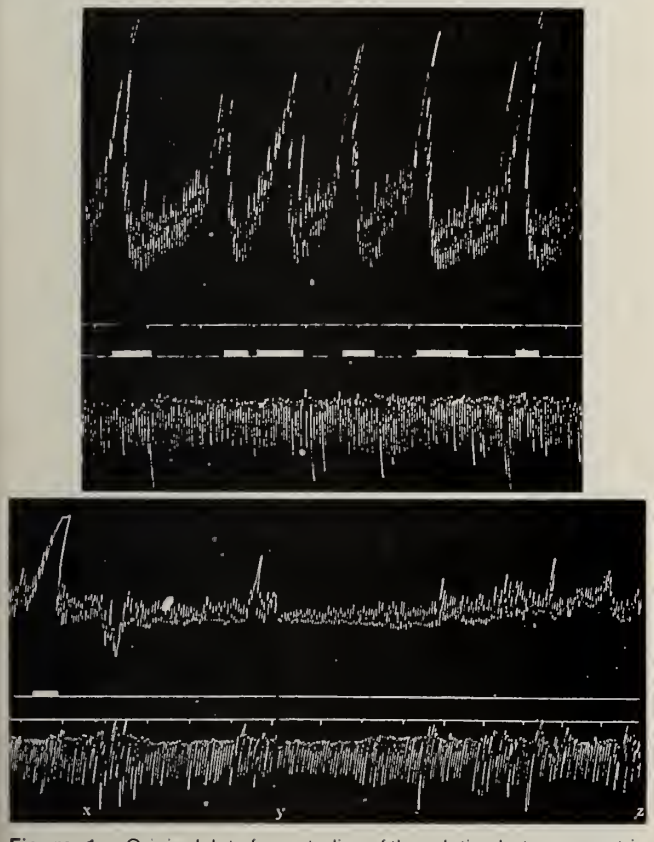

Figure 1.—Original data from studies of the relation between gastric activity and hunger sensations. The upper panel shows large stomach contractions (uppermost trace). Time signal is in 0.1 minutes (second trace). Key depressions indicate that subject felt hunger pangs (third trace) and respiration is shown (bottom trace). The lower panel is similar to the upper panel except there are few gastric contractions and few signals of the presence of hunger pangs (from Cannon[28]).

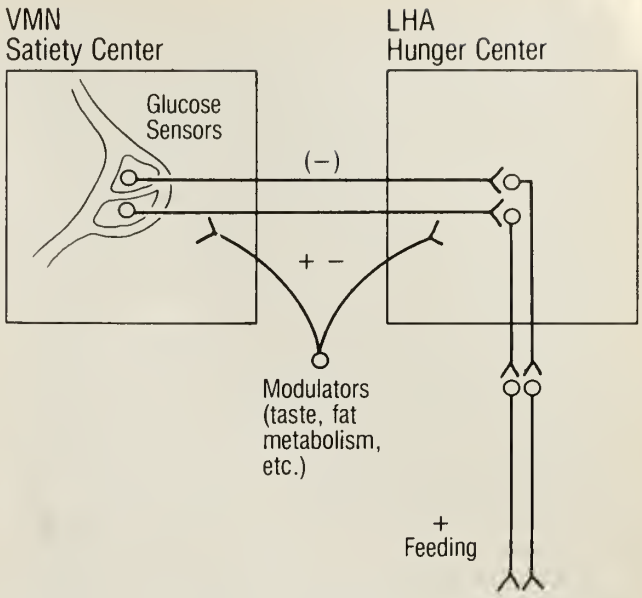

Figure 2.—A schematic of the glucostatic dual-center hypothesis. Ventromedial hypothalamic nuclei (VMN) satiety centers exert an inhibitory control over a lateral hypothalamic area (LHA) hunger center.

Peripheral and central loci for feeding control. The third phase in feeding research, begun in the 1960s, has been characterized by the attempt to find the organ, or area within or peripheral to the brain, that primarily controls feeding.

Oral factors play a major role in feeding. Although it was thought that they were dispensable, even that is not so clear.[30] Palatability cues exert great influence over energy intake. One can, for example, alter the level at which body weight is regulated by altering the palatability of the available food, an observation clearly shown in animals[31] and no doubt equally the case in humans.

Recently, Deutsch has resurrected the hypothesis that the stomach is a major source of signals controlling feeding.[32] He showed that food need only reach the stomach to provide potent quantitatively meaningful control over feeding. The implication for satiety is that food need not reach the gut nor even be absorbed (and reach other visceral organs or the brain) to provide adequate cues of satiety. Nevertheless, after gastrectomy, hunger as a sensation is retained and relatively normal body weight maintained.

The gut has also been implicated in feeding. One can introduce nutritive material via an intraduodenal cannula bypassing mouth and stomach and reduce subsequent intake. In some cases, this reduction may well be due to sickness or nausea, but in other situations it is likely that true satiety is induced. When hyperosmolar solutions such as 20% glucose are infused into the gut, sickness does ensue. On the other hand, isosmolar nutrient solutions such as 5% glucose will not cause malaise but will suppress food intake.[33] In addition, metabolic receptors have been found electrophysiologically in the gut.[34]

Russek proposed that the liver was the primary organ controlling food intake.[35] Again, it seems reasonable for the liver to be intimately involved in feeding control, particularly if one thinks of glucose metabolism as a primary concern of the feeding mechanism (the glucostatic hypothesis). The liver is the first line of defense of glucose homeostasis. It stores glucose when it is in excess (glycogenesis) and releases glucose molecules (glycogenolysis) or manufactures them (gluconeogenesis) when there is a need for glucose. The liver is also the first organ to sample much of the metabolite influx after absorption from the gut.

The hepatic theory of hunger and satiety has been controversial.[36] As in the gut, nutrient receptors are also present in the liver.[37] Interruption of pathways thought to innervate these receptors has been shown to alter feeding behavior.[38] Other investigators have found no effects of either putative complete liver denervation[39] or bypassing the liver after portacaval shunt.[40] Findings of experiments involving intravenous infusions of 2-deoxy-D-glucose, which blocks glucose uptake and use, have affirmed the liver's role in feeding. A shorter and more powerful hunger-inducing effect occurred when a hepatic-portal route was used compared with a systemic one.[41] Infusing nutrients such as glucose has yielded ambiguous results. At present, the role of the liver in controlling feeding remains moot.

Finally, the brain is also involved. The central nervous system (CNS) contains nutrient receptors, which are present in the hypothalamus and brain stem.[42] The existence of hypothalamic glucose-sensitive neurons strongly supports the dual-center glucostatic hypothesis. The behavioral evidence linking the hypothalamic glucoreceptors with feeding, however, is mixed. Infusing glucose or 2-deoxy-D-glucose by intracranial cannula into the hypothalamus has not delimited structures clearly involved in feeding. The results of gold thioglucose administration, a substance presumed to damage selectively ventromedial hypothalamic glucoreceptors causing hyperphagia and obesity, have also supported,[43] or been irrelevant to, the hypothesis of hypothalamic glucoreceptor control of feeding.[44]

In this third phase of theorizing about feeding controls, extensive and useful strides were made to reestablish the importance of events peripheral to the brain. The search for a sole or even primary locus of control has not been successful. At all levels from mouth to brain, important effects on feeding may be shown but none of the effects can be documented to be necessary or even primary.

Circulatory Agents

The discovery of the many gut, visceral and brain peptides and hormones has suggested the possibility that one or more of these could be hunger and satiety signals. At present two seem outstanding: cholecystokinin and glucagon; others are insulin,[45] bombesin[46] and endogenous opioids.[47]

Cholecystokinin is released from the gut in response to many components of a meal and in small quantities it reliably suppresses normal and sham feeding.[48] The interpretation of the results of feeding studies, however, is controversial. Does administering cholecystokinin suppress feeding through a satiety mechanism[48] or by producing nausea and malaise?[32] It would help to know what a physiologic dose of cholecystokinin is but reliable radioimmunoassay of cholecystokinin in blood is still not available.

Administering glucagon (another possible satiety agent) to animals fed spontaneously suppresses subsequent intake.[49] Glucagon is released in response to ingesting some components of food.[50] This result might be surprising because of its steady rise during starvation. However, Langhans and associates[51] have clearly shown a meal-induced rise and involvement of the hormone in satiety by showing that glycogenolysis occurred after a meal. They also found that administering glucagon antiserum reduced hepatic vein glucose concentration and increased meal size and duration in rats when compared with a control series of infused rats.[52]

We have shown that administering glucagon suppresses food intake when an animal is only minimally deprived[49]; it fails to do so if the animal is deprived of food for a longer time. This suggests that glucagon's suppressive effect depends on its action in causing hepatic glycogenolysis. Geary and colleagues have found other evidence to support this.[53] Finally, Martin and Novin showed that the glucagon-induced feeding depression depends on vagal innervation[49]; it disappears after subdiaphragmatic vagotomy.[54]

Although glucagon's action on feeding is not due to induced illness,[49] more sensitive tests are needed. Because the dosages used in the glucagon studies are high, the feeding effects may be pharmacologic rather than physiologic.

Neural Messages

Nutrient availability is certainly coded by chemoreceptors innervated by the autonomic nervous system. The first of these, taste, is also the best known. Norgren and Leonard[55] have uncovered the central neural pathways of the gustatory sense. But what of other chemoreceptors?

Because of the continuity of the alimentary canal, it is not surprising that there is electrophysiologic evidence for chemoreceptors in the gastrointestinal tract.[34] There is similar evidence from visceral nerve recordings for hepatic chemoreceptors, for mechanoreceptors and osmoreceptors in the gastrointestinal tract[56] and osmoreceptors in the liver.[57] Most of these findings are from recordings of vagal (parasympathetic) efferents,[56] but afferents also travel with the sympathetics.[34]

Results of studies in rats show that some visceral receptor inputs project to areas overlapping, and even converging, with the gustatory system (Figure 3).[37,55,58] The anterior pole of the nucleus tractus solitarius is the first relay nucleus of the gustatory system.[55] Visceral afferents project to a posterior region of the same nucleus some millimeters removed from the gustatory projections. Although these two systems do not converge directly at this level, Hermann and associates[58] have shown that both areas receive and give projections to the adjacent reticular formation. The next relay is at the pons in the parabrachial nucleus, the area Norgren and Leonard initially called the pontine taste area.[55] Hermann and co-workers[58] found that there are separate and convergent relays for gustatory and visceral inputs (Figure 3). In an earlier study, Hermann and Novin[59] showed that gustatory and visceral afferents converged in the parabrachial nucleus.

Grill and Norgren have shown that in rats this level of the neuraxis can subserve some surprisingly complex feeding behavior.[60] Normal rats characteristically accept palatable and reject unpalatable substances; these same responses are seen in decerebrate rats where everything above the pons is disconnected. Moreover, when satiated, decerebrate rats reject even previously palatable solutions, just as brain-intact rats do.

From the parabrachial nucleus both visceral and gustatory senses project to the ventrobasal complex of the thalamus, the analog of the classical sensory pathway. In addition, the parabrachial nucleus projects to hypothalamic and limbic system structures and directly to the cortex. Visceral afferents, particularly from an hepatic glucose-sensitive system, converge onto iontophoretically identified glucose-sensitive cells in the lateral hypothalamus.[61] Thus, at the hypothalamic level central and peripheral nutrient receptors interact.

Behavioral evidence shows that this level is required for even simple learning about taste-visceral connections. Thus, an intact animal will easily learn to reject even innately palatable tastes that are followed by an induced illness. A decerebrate rat does not learn this.[60] Ventrobasal complex lesions alone also prevent this type of learning. It seems, then, that behavior requiring "hard-wired" gustatory-visceral connections need only use brain-stem circuitry, whereas learned modifications of feeding behavior require higher levels of the nervous system. Whereas thalamic and hypothalamic mechanisms are all that are needed to subserve simple learning, long-term retention of learned feeding behavior may require the cortex (Philip S. Lasiter, PhD, Department of Psychology, UCLA, oral communication, March 1983).

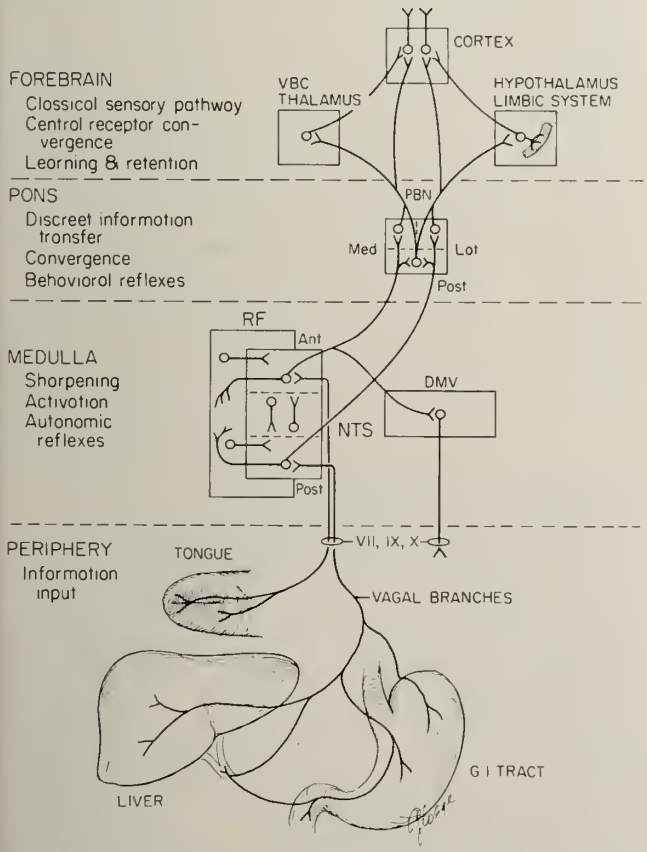

Figure 3.—A schematic of our current knowledge of the gustatory and visceral afferent pathways—the neural circuitry of feeding—in the brain. This suggests a hierarchy of processing, more complex information and behavior being subserved by higher levels of the neuraxis. (Adapted from Niijima,[37] Norgren and Leonard,[55] Hermann et al[58] and P. S. Lasiter, PhD, Department of Psychology, UCLA, and R. C. Rogers, PhD, Department of Physiology, Northwestern University Medical School, Evanston, Ill, oral communication, March 1983). DMV = dorsal motor nucleus of the vagus, G.I. = gastrointestinal, NTS = nucleus of the tractus solitarius, PBN = parabrachial nucleus, RF = reticular formation, VBC = ventrobasal complex

Much still needs to be learned about the neural substrates of feeding and their behavioral correlates. Nevertheless, several points are suggested by our current knowledge of these central pathways. At all levels of the CNS there is accurate information transfer and perhaps sharpening. At the same time, information may converge from different but equally relevant inputs as one ascends the nervous system. Simple autonomic and behavioral reflexes are organized at rather low levels of the CNS, some of which require integration of gustatory and visceral inputs. Learned behaviors and behavior involving complex integration need diencephalic structures. Long-term retention of learned feeding behaviors may require the highest levels of the nervous system, the cortex. Feeding may be controlled by various neural mechanisms of increasing flexibility and complexity. It would, therefore, be useless to seek *the* feeding or satiety center. Feeding seems to be the result of widely connected peripheral and central neural structures subserving different aspects of feeding behavior.

Integrated Systems Approach

There seems to be good evidence that the entire upper alimentary canal, the liver and the brain provide input important in feeding regulation. Equally compelling is the evidence that none are necessary components of that regulation, except insofar as they are necessary for life. These arguments are outlined above.

If this is so, it strongly suggests a redundant system of multiple inputs. More than that, it is useful to recognize that alimentation is a sequence in which each step in the process is involved in preparing the next stage to function more adequately. Thus, the cephalic phase of secretion causes gastrointestinal and pancreatic activity that greatly aids in the proper use of ingested metabolites. None of the organs of alimentation or metabolism operates in isolation. This interdependence may be why it is so often difficult to assess the role on feeding of an isolated organ. For example, it is difficult to show that hepatic glucose infusion alone suppresses subsequent intake. In contrast, when oral intake is combined with hepatic infusion, the contribution to the suppressive effect of each on carbohydrate intake is clear (D. Novin, PhD, unpublished data, May 1984).

Consideration of the information transfer and processing reinforces the notion that we have to broaden our perspective from thinking of specific signals, isolated organs or neural "centers." The evidence suggests that the brain integrates diverse feeding information in a hierarchical organization. Simple behaviors and autonomic reflexes of considerable importance use the lowest levels of the neuraxis based on the afferent inputs organized at that level. As the behavior gets more complex, increasingly complex afferent input and integration are probably required and involve higher and higher levels of the nervous system.

To understand the complexities of feeding, we need to study how the relevant signals (taste, visceral senses and so on) are processed by those organs involved in feeding. It is also vital to know how this information is projected to and integrated by the brain to produce the finely tuned behavior that it is for most organisms. For a clinician involved in treating feeding disorders, this approach is the one most likely to lead to an understanding of why this complex and elaborate system, viable for most, so often fails in humans and leads to pathologic states.

Experimental Gastric Ulceration After Lateral Hypothalamic Lesions

CARLOS V. GRIJALVA, PHD:* Although the cause of peptic ulcer is not well understood, it is thought that psychologic factors play a prominent role in the pathogenesis of some forms of the disease. Both clinical and experimental observations suggest that stress is a contributing factor[18]; a direct link between stress or other psychologic states and peptic ulcer disease remains to be elucidated, however.[62]

To identify the psychologic and behavioral components underlying peptic ulcer disease, some investigators have developed animal models that use various stress-provoking procedures. Although these approaches have been useful in showing an association between external or environmental factors and the presence of gastroduodenal abnormalities, the significance of this association remains equivocal because the underlying assumptions about what constitutes stress vary widely across experiments.

A different approach to studying the psychologic components to stress and peptic ulcer disease has been to examine the role of the nervous system. Although considerable advances have been made in establishing the relation between the central and autonomic nervous systems and gastrointestinal functions, our knowledge of the relative importance of specific brain regions and neural pathways remains fragmentary. Several cortical and subcortical structures have been implicated in the mediation of gastrointestinal functions, but most investigations have concentrated on the hypothalamus and its associated pathways.[15,63] This is not surprising given the close anatomic and functional relation between the hypothalamus and autonomic-endocrine systems.[64] One area of the brain that seems to be intimately involved in ingestive and digestive functions is the lateral hypothalamus.

Lateral Hypothalamus and Ingestion

The lateral hypothalamus has long been thought of as the feeding center because electrical or chemical stimulation of the lateral hypothalamus could induce eating in satiated animals and because damage to this area produced severe feeding and drinking deficits that seemed to be a function of the amount of lateral hypothalamic tissue destroyed.[65] It is now well established that although neurons within the lateral hypothalamic area may participate in ingestive behaviors, many of the acute and chronic dysfunctions in feeding and drinking after damage to the lateral hypothalamus are due to disruption of fibers of passage coursing through the area.[66] Furthermore, many of the effects that such lesions have on ingestive behaviors are closely related to alterations in general metabolism, energy homeostasis and autonomic functions.[67]

Lateral Hypothalamic Involvement in Gastric Acid and Gastrin Secretion

The results of several studies indicate that the lateral hypothalamus is involved in gastric acid secretion. In 1966 Misher and Brooks reported that electrical stimulation of the lateral hypothalamus in rats increased gastric secretion and acidity, which could be abolished by bilateral vagotomy.[68] Osumi and colleagues replicated this initial finding and further showed that electrical stimulation of the lateral hypothalamus also increased gastric mucosal blood flow.[69] Electrical stimulation of the lateral hypothalamus in cats also has increased gastric acid secretion, but these effects seem equivocal.[70]

Several studies provided additional support for lateral hypothalamic mediation of gastric acid release. For example, Colin-Jones and Himsworth showed that gastric acid secretion in rats was increased after administering 2-deoxy-D-glucose to the lateral hypothalamus.[71] This increase was prevented by raising the blood glucose concentration and by vagotomy. In addition, increases in gastric acid secretion induced by insulin or 3-0-methyl-glucose could be blocked by anesthetization of the lateral hypothalamic area with phenol or lidocaine.

Davis and associates found that lesions of the lateral anterior hypothalamus in dogs produced a significant increase in basal gastric acid secretion and these lesions blocked the gastric hypersecretory response to insulin.[72] Lesions placed just medial (paraventricular region) to the lateral anterior hypothalamus did not affect gastric secretion. In cats, lesions of the lateral hypothalamus and medial forebrain bundle have attenuated or abolished the increases in gastric acid secretion induced by insulin hypoglycemia or cytoglucopenia caused by systemically administered 2-deoxy-D-glucose.[73] Lesions placed immediately rostral, medial or dorsal to the lateral hypothalamus do not seem to alter the effect of 2-deoxy-D-glucose on gastric secretion. Michael Ruppel, MA, and Ernest Lindholm, PhD, Arizona State University, found that the initial periods of aphagia or hypophagia in rats resulting from lateral hypothalamic lesions were associated with increases in the volume of gastric secretion (unpublished data, December 1976). We have recently shown that the gastric secretory volume and acidity are significantly increased within two hours after lateral hypothalamic lesions.[74] On the other hand, Opsahl and Powley suggest that the long-term effect of lateral hypothalamic damage in rats is to reduce basal levels of gastric acid secretion.[75] These findings indicate that the immediate effects of lateral hypothalamic lesions may be related to an abrupt increase in neural activity of cells affected by the irritative property of electrolytic lesions and, thus, may mimic the effects of electrical stimulation.

Apart from electrical stimulation or lesions studies, there is evidence suggesting that the lateral hypothalamic area may be a site of action for certain neuropeptides that are implicated in the regulation of gastric secretion. Tepperman and Evered showed that microinjections of pentagastrin or natural gastrin into the lateral hypothalamus of conscious rats significantly increased gastric acid secretion, which could be blocked by atropine and by vagotomy.[76] Furthermore, similar doses injected intravenously or into other forebrain structures did not affect gastric secretion. Intrahypothalamic infusions of neurotensin, substance P and vasoactive intestinal polypeptide did not alter gastric secretion; infusions of bombesin into the lateral hypothalamus, however, decreased gastric acid output.

Both gastrin and bombesin may exert their effect by influencing neurons within the lateral hypothalamus; it is unlikely, however, that the lateral hypothalamus is the only site of action for these peptides. We have shown that intracisternal injection of bombesin, a tetradecapeptide originally isolated from the skin of frogs and found in mammalian gut and brain,

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attenuates the increase in gastric acid secretion induced by acute lateral hypothalamic lesions.[74] Intracisternal injections of bombesin, however, significantly increase circulating levels of gastrin,[77] and lateral hypothalamic lesions block this effect (Figure 4). Bilateral parasagittal knife cuts placed lateral to the lateral hypothalamus or coronal knife cuts placed posterior to the lateral hypothalamus also had similar effects on bombesin-induced hypergastrinemia.[78] These findings suggest that although the lateral hypothalamic area is not necessary for the expression of the inhibitory action of bombesin on gastric acid secretion, it seems to be directly involved in the effects that bombesin exerts on circulating levels of gastrin.

Lateral Hypothalamus and Gastric Mucosal Damage

In their initial studies on feeding behavior after lateral hypothalamic lesions, Teitelbaum and Epstein found on postmortem examination of rats who had died after a period of aphagia that some animals showed massive stomach ulceration and hemorrhage.[29] Although the gastric ulcers reported by them may have been related to the effects of starvation induced by lateral hypothalamic damage, in 1975 Lindholm and colleagues showed that bilateral lateral hypothalamic lesions (Figure 5) induced gastric mucosal damage within 24 hours postoperatively.[79] The severity increased during a four-day postoperative observation period, and this effect could not be accounted for by food and water deprivation alone. Furthermore, similar-sized lesions of the overlying thalamus did not induce gastric ulcers.

In further studies in our laboratory, we examined the effects of preoperative weight reduction on the incidence of gastric mucosal damage induced by lateral hypothalamic lesions. In one study[80] the weights of rats were reduced slowly by restricting daily food intake for two weeks, or rapidly by fasting totally for six days. Both groups of rats were reduced to the same body weight before lateral hypothalamic lesions were made. Rats either maintained at a normal body weight or preoperatively rapidly starved to 80% of their normal body weight showed ulcers and erosions of the glandular portion of the stomach after lateral hypothalamic damage. Rats preoperatively dieted slowly to 80% of their normal weight showed virtually no gastric ulceration after the brain damage. In addition to gastric ulcers, rats with lateral hypothalamic lesions showed hypersalivation, abnormal lacrimation and hyperthermia. We found that preoperative weight reduction from 5% to 25% of normal weight produced by dieting regimens was enough to attenuate these disorders to varying degrees.[81] Lateral hypothalamic lesions are associated with initial increases in metabolic rate; restricted feeding schedules, which reduce body weight, may provide some protection by altering the metabolic rate.

In attempting to elucidate some of the possible mechanisms underlying gastric mucosal damage after lateral hypothalamic lesions in rats, we have shown that the incidence of gastric erosions can be reduced significantly by subdiaphrag-

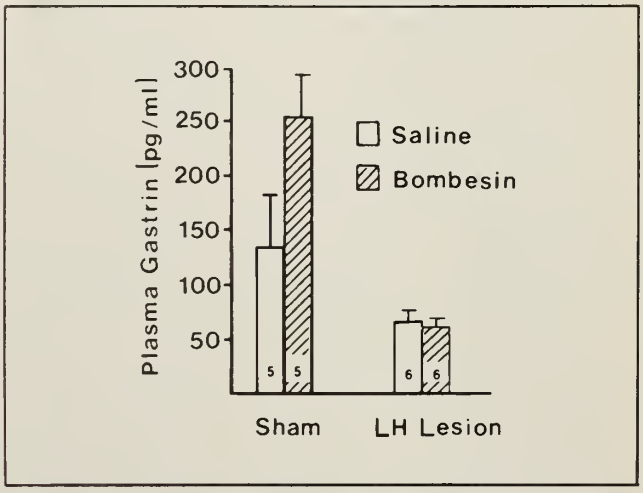

Figure 4.—The effect of intracisternal administration of bombesin (500 ng) alone or in combination with lateral hypothalamic (LH) lesions on blood gastrin in rats. Columns represent means and standard errors.

Figure 5.—Photomicrograph of a coronal section taken through the rostrocaudal midpoint of bilaterally placed lateral hypothalamic lesions in a rat. The brain lesions are indicated by arrows (thionin stain, original magnification × 6).

matic vagotomy or by administering propantheline bromide (anticholinergic), cimetidine (H_2-receptor antagonist)[82] or the antimuscarinic agent, pirenzepine,[83] all of which reduce gastric acid secretion. Only propantheline bromide also prevented the occurrence of hypersalivation and increases in lacrimation, indicating that a primary effect of lateral hypothalamic lesions is to produce an abrupt increase in parasympathetic activity. Tordoff and colleagues examined the effects of splanchnicectomy, celiac ganglionectomy, adrenal demedullation, adrenalectomy or chemical sympathectomy with guanethidine on gastric ulceration induced by a lateral hypothalamic lesion and found that none of these procedures significantly altered the severity of ulceration.[84]

Gastric acid is an essential factor in the production of peptic ulcer, but abnormally high levels of acid or pepsin are not always found. The extent to which the aggressive action of gastric acid and pepsin is pathologic partly depends on the defensive properties of the gastric mucosal barrier. The gastric mucosal barrier has been defined as the property of the gastric mucosa that impedes diffusion of acid from the lumen into the mucosa and impedes diffusion of sodium ions from the mucosal interstitial space into the lumen. We recently reported that significant changes in gastric mucosal barrier functions occurred within as little as three hours after lateral hypothalamic lesions.[82] These changes were indicated by a small but significant reduction in gastric transmucosal potential difference and a significant increase in hydrogen ion loss and sodium gain from the gastric contents. Furthermore, when sacrificed three hours postoperatively, only two of seven rats with lateral hypothalamic lesions showed gross gastric defects, whereas all seven rats showed similar alterations in barrier functions. Werther and Horowitz have reported similar changes in gastric mucosal barrier properties after restraint-stress in rats,[85] suggesting that both restraint-stress and certain forms of brain damage may produce gastric abnormalities by inducing similar pathophysiologic changes in the gut.

Gastric ulceration and gastritis have also been associated with the reflux of bile into the stomach that, in turn, seems to be related to the effects that bile salts have on the gastric mucosal barrier. Gastric mucosal damage in rats induced by lateral hypothalamic lesions can be blocked by bile duct ligation.[86] This finding suggests that the reflux of bile into the stomach in animals with lateral hypothalamic lesions may interact with a weakened gastric mucosal barrier to facilitate erosion and ulceration.

Studies are currently in progress to investigate some of the possible limbic system structures and neural pathways mediating the effects that lateral hypothalamic lesions have on the gastrointestinal tract. In a series of studies Henke has shown that the severity of gastric ulcers in rats can either be attenuated or facilitated by lesions in different structures with the limbic system.[87] One limbic system structure that has been implicated in emotionality and responsivity to stress is the amygdala. The severity of gastric ulceration in rats produced by physical restraint could be attenuated by prior lesions of the centromedial amygdala. Recent autoradiographic studies have shown ascending projections from the lateral hypothalamic area to the region of the central nucleus of the amygdala in rats.[88] This anatomic connection between the lateral hypothalamus and amygdala seems to be functionally related to gastric processes. We produced bilateral electrolytic lesions of the centromedial amygdala in 12 rats, while another group of 12 rats underwent a sham operation (C. Grijalva, PhD, and P. J. Geiselman, PhD, unpublished data, March 1980). Six to eight weeks later both groups were given bilateral lateral hypothalamic lesions, fasted for 24 hours postoperatively, sacrificed and their stomachs examined for abnormalities. Figure 6 shows an example of the combined lateral hypothalamus and amygdaloid lesions. Prior centromedial amygdaloid lesions (Figure 7) significantly attenuated the severity of gastric mucosal damage induced by lesions of the lateral hypothalamic area. We have recently found that centromedial amygdaloid lesions reduce gastric acid secretion,[89] and this may be a mechanism by which these brain lesions exert their protective effect on both stress-induced and hypothalamically induced gastric ulcers.

The lateral hypothalamic area in various species is inti-

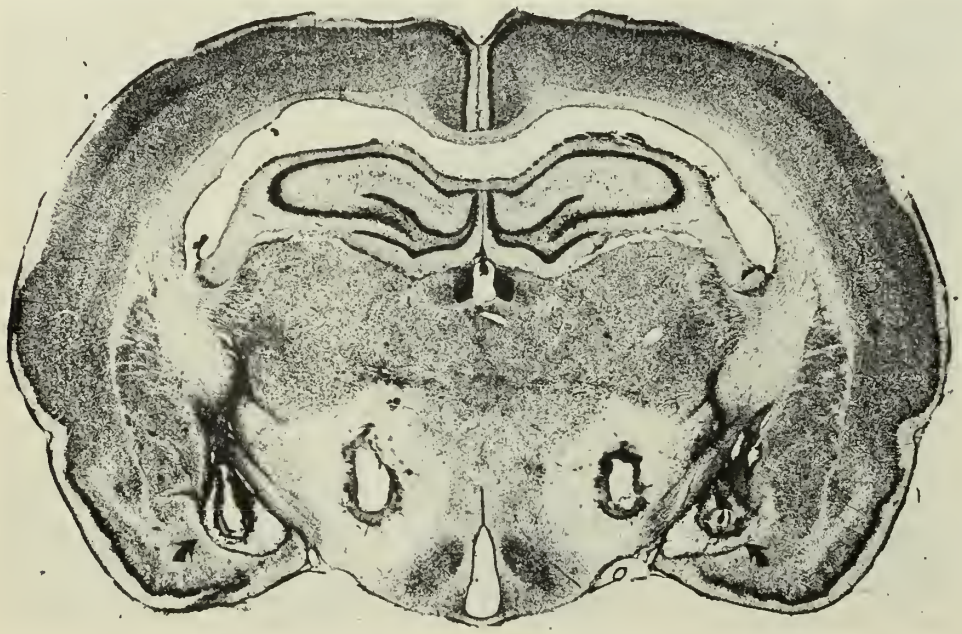

Figure 6.—Photomicrograph of a coronal section taken through the rostrocaudal midpoint of bilaterally placed centromedial amygdaloid lesions (indicated by arrows) and lateral hypothalamic lesions in the rat (thionin stain, original magnification × 6).

mately involved in regulating gastrointestinal function. Part of this involvement may be mediated by its connection with the autonomic nervous system and by its anatomic connections with limbic system structures implicated in emotional behaviors. The extent to which one can extrapolate findings in animal models to those in humans is presently unclear; however, studies such as the ones described may elucidate some of the underlying neural, peptidergic and behavioral processes involved in certain forms of peptic ulcer disease in humans.

Role of Brain Neuropeptides in the Regulation of Gastric Secretion

YVETTE TACHÉ, PHD:* During the past decades, literature reviewed by Grijalva and associates showed that electrical stimulations, or lesions of discrete brain area, elicited pronounced gastric morphologic and secretory changes. In these studies specific nervous structures and pathways influencing gastric function and the development of ulceration were identified. Little was known, however, about the biochemical signals acting on these brain sites that trigger gastric changes. Recently, the identification of neuropeptides in the brain and the gastrointestinal tract as a new class of intercellular messengers has given new impetus for understanding brain-gut interaction. We will focus on how neuropeptides influence gastric secretion (Table 1).

Neuropeptides That Stimulate Gastric Acid Secretion

Gastrin. The injection of pentagastrin (77 ng) into the lateral hypothalamus produced a transient increase of gastric acid output in rats with a gastric fistula. This response seemed to be specific for the lateral hypothalamus and was blocked by vagotomy or atropine, suggesting vagal-dependent neural pathways mediating gastrin's action.[76] However, gastrin (0.1 to 5 μg) or pentagastrin (0.2 μg) injected into the cerebrospinal fluid at the level of the cisterna magna or the lateral ventricle did not influence gastric secretion.[76,77,90]

The significance of gastrin acting centrally to stimulate gastric secretion has to be reconsidered because of the recent chemical identification of cholecystokinin 8 (CCK 8) in the brain. CCK 8 shares with gastrin complete homology of the C-terminal pentapeptide fragment and has accounted for the so-called gastrinlike immunoreactivity reported earlier in the brain.[91] Studies with the naturally occurring CCK 8 peptide, for which specific receptors have been found in the brain,[9] are needed to ascertain a possible central action of the cholecystokinin-gastrin family in controlling gastric secretion.

Somatostatin analogs. Intracisternal injection of some oligosomatostatin analogs, like des-AA^{1,2,4,5,12,13} [D-Trp^{8}] somatostatin (ODT8-SS), increased the volume and acid output of gastric secretion in rats. No effect was found after systemic administration of the peptide. The stimulatory action of intracerebrally injected ODT8-SS was dose-dependent (0.1 to 1 μg), reversible, long lasting, specific and abolished by vagotomy or systemic administration of atropine.[93] Because intracisternally injected somatostatin 14 or 28 did not influence gastric secretion, these results raise the question of whether the reduction in chain length of somatostatin enhanced the penetration of the oligosomatostatin analogs to their sites of action on somatostatin receptors in the brain or, alternatively, whether such effects are unique selective properties of the peptides acting on other receptors unrelated to somatostatin.

Thyrotropin-releasing hormone (TRH). The tripeptide TRH, given intracisternally or intracerebroventricularly, greatly increased gastric secretion in rats.[94] The stimulatory action is rapid at onset, dose dependent (0.1 to 3 μg), long acting, reversible and is found in conscious or urethane-anesthetized rats (Figure 8).[94] The most stable TRH analog, *p*-Glu-His-(3,3′dimethyl)-Pro-NH_2, RX 77368, mimicked the effects of TRH, but could elicit gastric secretion at a dose as low as 3 ng given intracisternally in urethane-anesthetized rats with a gastric fistula.[95] Although some CNS effects of TRH are exerted by its metabolites, the CNS action of the peptide on gastric secretion is mediated by TRH itself.[95] The neurohumoral pathways through which TRH stimulated gastric acid secretion are unrelated to its hypophyseotropic effects but appear to be vagal dependent and expressed through cholinergic mechanisms.[94,95] This is further supported by evidence that TRH injected intracisternally increased vagal efferent discharges recorded from platinum electrodes hooked to the truncal vagal nerve.

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TABLE 1.—*Central Nervous System Action of Neuropeptides in Influencing Gastric Secretion in Rats*

Neuropeptides	*Gastric Acid Secretion*
Inhibitors	
Bombesin-like peptides	↓
Calcitonin	↓
Calcitonin gene-related peptide	↓
Corticotropin-releasing factor	↓
Neurotensin	0 ↓
Opioid peptides	↓
Stimulants	
Gastrin	0 ↑
Somatostatin analog ODT8-SS	↑
Thyrotropin-releasing hormone	↑

↓ = inhibition; ↑ = increase; 0 = no effect

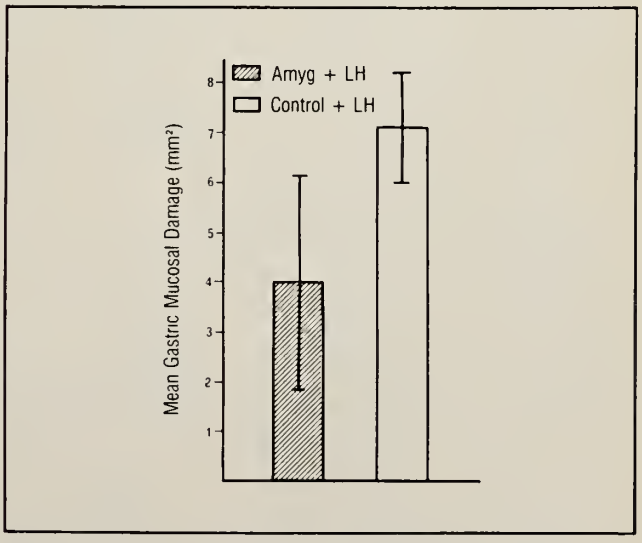

Figure 7.—This graph depicts the mean total area of glandular gastric mucosal damage in rats (N = 12 rats per group) sustaining either bilateral centromedial amygdaloid lesions (Amyg) and subsequent lateral hypothalamic (LH) lesions, or lateral hypothalamic lesions only. Both groups were examined for gastric abnormalities 24 hours after the lateral hypothalamic lesions.

High levels of TRH and its receptors have been characterized in the hypothalamus[96] and in the nucleus of the vagal complex,[97] providing a neuroanatomic substrate for confirming the role of brain TRH in modulating gastric function.

Neuropeptides That Inhibit Gastric Acid Secretion

Neurotensin. This tridecapeptide was isolated from the hypothalamus and like other neuropeptides, has a characteristic distribution with a highly individual neuronal circuitry in hypothalamic and extrahypothalamic structures. Autoradiographic localization of neurotensin-binding sites paralleled that of the regional distribution of the peptide.[98]

Neurotensin was the first peptide reported to decrease basal gastric acid secretion after intracerebroventricular administration (1 to 10 μg) in urethane-anesthetized rats with a gastric fistula. Neurotensin action was abolished by 6-hydroxy dopamine or reserpine pretreatment, suggesting that central catecholamines are mediating neurotensin's action on gastric secretion.[99] Japanese investigators found that neurotensin injected into the lateral hypothalamus (0.5 μg) transiently suppressed insulin-induced acid secretion.[100] Those findings have not been confirmed by American groups, however.[76,101] Whether neurotensin in the brain may play a role in the control of gastric acid secretion remains questionable.

Bombesin-like peptides. Bombesin is a tetradecapeptide originally isolated from the skin of the frog, *Bombina bombina.* Its mammalian counterpart has been chemically characterized from porcine gut and called gastrin-releasing peptide. This 27-residue peptide shares a C-terminal decapeptide homology with the C-terminal decapeptide fragment of bombesin, except for an interchange of Gln/His in position 7.[102] Bombesin-like peptides are widely distributed in mammalian brain and spinal cord.[103,104] The specific binding of bombesin to rat brain membrane and the regional distribution of bombesin receptors have been described.[105]

Bombesin or gastrin-releasing peptide injected intracisternally greatly reduced gastric secretory volume and titratable acidity in rats.[77] The inhibitory action of the peptides was long lasting, reversible, specific and dose-dependent in doses ranging from 0.01 to 1 μg in rats. Doses of bombesin as low as 10 ng decreased by 60% gastric acid output; higher doses (0.5 to 1 μg) raised gastric pH values above neutrality in pylorus-ligated rats. The biologic activity of gastrin-releasing peptide is contained in the C-terminal octapeptide fragment of the molecule.[77] Bombesin injected into cerebrospinal fluid suppressed acid secretion in various animal species: albino or hooded rats,[74] cats[106] and dogs[107] studied either in a conscious state or anesthetized with ether, methohexital sodium, urethane or chloralose. Figure 9 shows that bombesin or gastrin-releasing peptide blocked or decreased gastric acid output stimulated by different secretagogues such as 2-deoxy-D-glucose, insulin, histamine,[77] pentagastrin, TRH,[77] γ-aminobutyric acid agonist muscimol and baclofen, prostaglandin E_2, ODT8-SS or cysteamine and by various surgical manipulations, such as pyloric ligation, acute lesions of the lateral hypothalamus, lesions of the ventromedial hypothalamus, gastric sympathectomy or electrical vagal stimulation.

The pathways through which bombesin exerted its action are CNS mediated because the peptide inhibited acid secretion when injected into the cerebrospinal fluid at the level of either the lateral or the fourth ventricle or the cisterna magna,[77,106,107] but not when given intravenously.[77,106] In further studies done in rats to explore brain sites sensitive to bombesin, the peptide produced a pronounced rise in gastric pH values and a decrease in secretory volume when microinjected into the paraventricular nucleus; injections into other hypothalamic nuclei (lateral, ventromedial) or other forebrain structures, however, failed to alter gastric secretion.[108] Using centrally acting specific receptors or synthesis blockers of biogenic amines, we have not been able to prove that bombesin's influence involved an interaction with brain catecholamine, dopamine or serotonin neurotransmitters.[109] Bombesin action on gastric acid secretion seems unrelated to other effects of the peptide on pituitary and adrenal secretion.[109] Cross-circulation experiments showed that gastric response to intracisternal administration of bombesin is not mediated

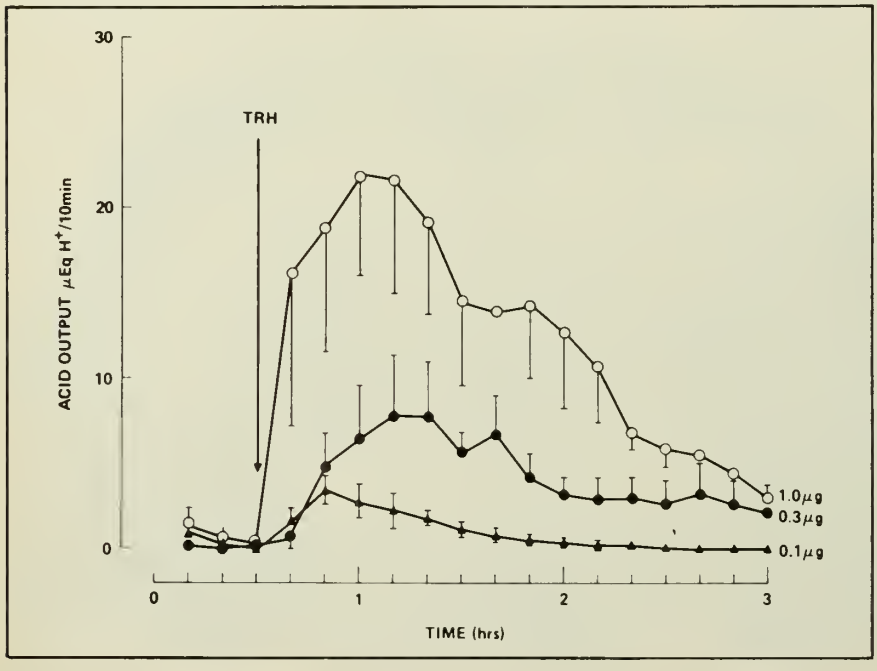

Figure 8.—Thyrotropin-releasing hormone (TRH), 0.1 to 1 μg injected intracisternally, stimulated gastric acid secretion in urethane-anesthetized rats with a gastric fistula. One hour after placement of a gastric fistula, the gastric lumen was flushed every 10 minutes with two 5-ml boluses of 0.15 mol per liter of sodium chloride and one 5-ml bolus of air. Acid output was determined by titration to pH 7.0 of the flushed perfusate. Each point represents the mean ± standard error of the mean of five to eight rats.

by humoral mechanisms. Bombesin effects were also independent of interaction with opiate receptors, prostaglandin generation and vagal activity. Pharmacologic and surgical approaches point to a mediation by the sympathetic nervous system because transection of the spinal cord up to the seventh cervical levels, or blockage of α_2- but not α- or β-adrenergic receptors, partly reversed the rise in gastric pH induced by intracisternal administration of bombesin.

Opioid peptides. The brain contains at least three anatomically separated neuronal networks of opioid peptides: an enkephalin, a β-endorphin and a dynorphin family.[110] Several distinct types of receptors (μ, γ, κ) for opiates have also recently been characterized in the brain.

The β-endorphin injected intracerebroventricularly or intracisternally inhibited gastric acid secretion in rats by decreasing gastric secretory volume and, to a lesser degree, titratable acidity under basal or TRH-stimulated conditions. The effect is dose dependent, in doses ranging from 0.8 to 25 μg, with 50% inhibition obtained with a 2.3 μg dose[111] and reversed by vagotomy.[112] The stable enkephalin analogs, D-Ala^2-Met-enkephalinamide (1 to 20 μg) or [D-Ala^2,Met-Phe^4,Met-(0)^{5}ol] enkephalin, FK33-824 (2 μg), injected intracerebroventricularly in rats suppressed gastric secretory volume and titratable acidity under a basal, TRH-, insulin- or muscimol-stimulated condition.[113] The tridecapeptide dynorphin (1 μg) has also produced similar inhibitory effects.[113]

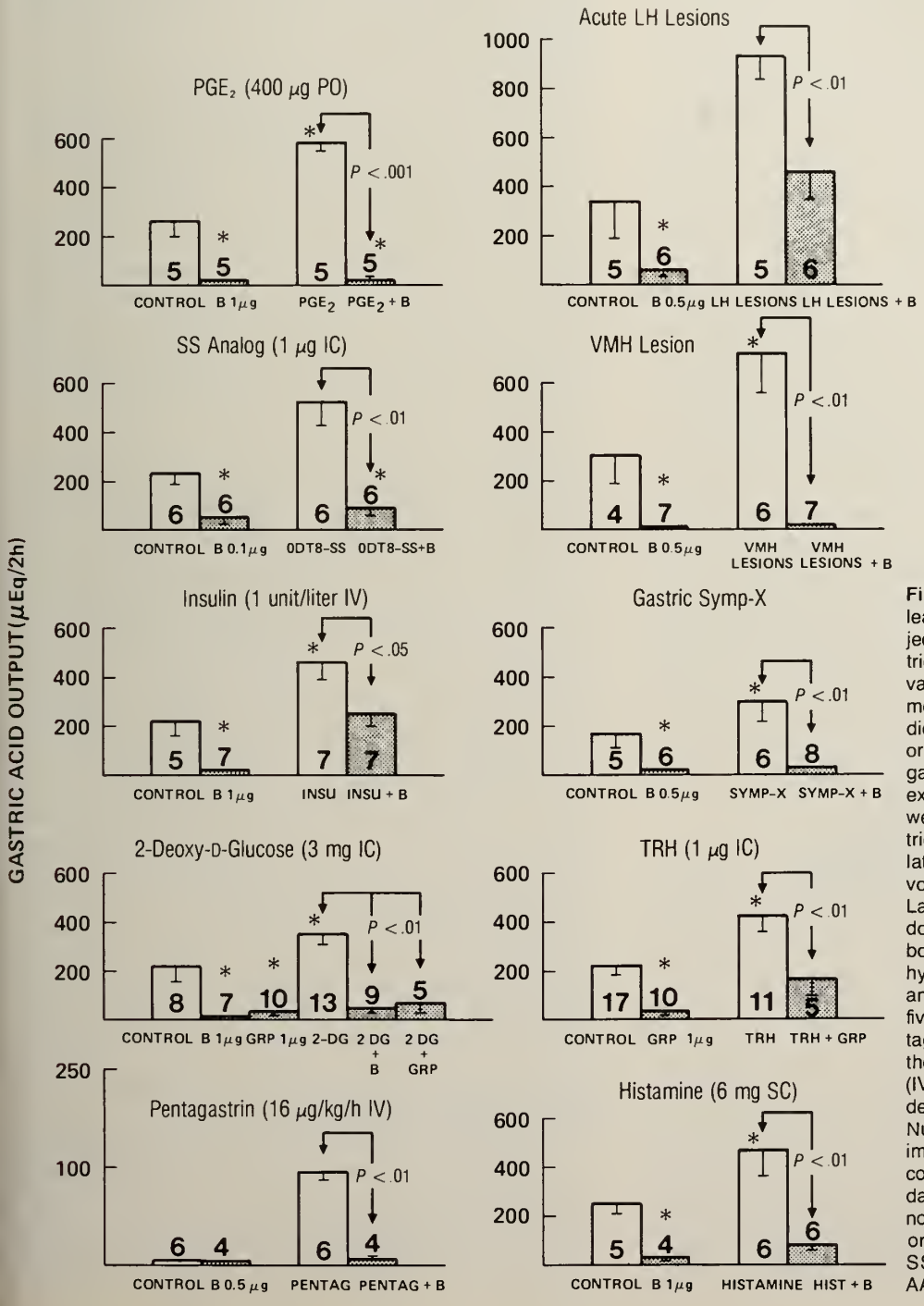
GASTRIC ACID OUTPUT (μEq/2h)
PGE₂ (400 μg PO)
CONTROL B 1μg PGE₂ PGE₂ + B
P < .001
Acute LH Lesions
CONTROL B 0.5μg LH LESIONS LH LESIONS + B
P < .01
SS Analog (1 μg IC)
CONTROL B 0.1μg ODT8-SS ODT8-SS+B
VMH Lesion
CONTROL B 0.5μg VMH LESIONS VMH LESIONS + B
Insulin (1 unit/liter IV)
CONTROL B 1μg INSU INSU + B
P < .05
Gastric Symp-X
CONTROL B 0.5μg SYMP-X SYMP-X + B
2-Deoxy-D-Glucose (3 mg IC)
CONTROL B 1μg GRP 1μg 2-DG 2 DG + B 2 DG + GRP
TRH (1 μg IC)
CONTROL GRP 1μg TRH TRH + GRP
Pentagastrin (16 μg/kg/h IV)
CONTROL B 0.5μg PENTAG PENTAG + B
Histamine (6 mg SC)
CONTROL B 1μg HISTAMINE HIST + B

Figure 9.—Bombesin (B) or gastrin-releasing peptide (GRP) (0.5 to 1 μg) injected intracisternally (IC) inhibited gastric acid secretion stimulated in rats by various chemical and surgical treatments. Secretagogues were given as indicated, simultaneously with bombesin or GRP, and then the pylorus was ligated. Two hours later, conscious rats, except pentagastrin-treated animals, were decapitated for collection of gastric secretion. Acid output was calculated by multiplying gastric secretory volume by the concentration of acid. Lateral hypothalamic (LH) lesions were done within two to four minutes before bombesin administration, ventromedial hypothalamic (VMH) lesions four days and gastric sympathectomy (Symp-X) five days before peptide injection. Pentagastrin was infused in urethane-anesthetized rats through the jugular vein (IV) and gastric secretion collected as described in the legend of Figure 8. Number of rats for each treatment regimen is shown at the bottom. Each column represents the mean ± standard error of the mean. IV = intravenously; PGE_2 = prostaglandin E_2; PO = orally (per os); SC = subcutaneously; SS analog (ODT8-SS) = des-AA^{1,2,4,5,12,13} [D-Trp^8]

The gastric response to intracerebral injection of all opioid peptides was reversed by naloxone pretreatment.

The brain or spinal sites, types of receptors and neurohumoral pathways involved in mediating the inhibitory effects of opiates remain unknown. The influence of selective blockade in the brain of various opioid receptors on basal and stimulated gastric secretion will clearly show the physiologic role of brain opioid peptides in regulating gastric function.

Corticotropin-releasing factor (CRF). CRF is a 41-amino acid peptide recently characterized from the hypothalamus. The peptide plays a physiologic role in the control of pituitary secretion of adrenocorticotropic hormone and β-endorphin.[114] Hypothalamic and extrahypothalamic distribution of CRF-like immunoreactive neurons has been extensively studied.

CRF injected into rat cisterna magna induced a dose-dependent inhibition of gastric acid secretion by reducing acid concentration and, to a lesser degree, secretory volume. Peptide action was dose dependent in a dose range of 1 to 10 μg, long acting and observed in conscious or urethane-anesthetized rats. CRF inhibited acid secretion stimulated by pentagastrin or intracisternal administration of TRH.[115] Microinjection of CRF (0.2 to 4 μg) in the ventromedial and paraventricular nucleus, and to a lesser extent the lateral hypothalamus, induced an elevation of gastric pH values and secretory volume and a decrease of gastric acid concentration and output in pylorus-ligated rats.[116] The sites sensitive to CRF seem to be those shown to have the highest content of CRF-like immunoreactivity outside the median eminence. The neurohumoral mechanisms through which intracisternally administered CRF inhibited acid secretion are unrelated to its pituitary effects but seem to be reversed by adrenalectomy, vagotomy or spinal cord transection at the fifth to the seventh cervical levels. The CRF action on gastric acid secretion is, therefore, probably mediated by modulation of the autonomic nervous system, involving a decrease in vagal tone and an increase in sympathetic outflow.[115] The inhibitory action of intravenously administered CRF is seen at higher doses and mediated by different mechanisms.[117]

The physiologic role of CRF has yet to be elucidated, but it seems to mimic the cardiovascular, endocrine and behavioral responses to stress and alters gastric secretion in a manner similar to that of various stressors.[114,115] Therefore, CRF may play a role in the gastric response to stress.

Calcitonin and calcitonin gene-related peptides. Recently Rosenfeld and co-workers[118] showed tissue-specific alternative RNA processing pathways in the expression of the rat calcitonin gene, and predicted a 37-residue peptide called calcitonin gene-related peptide (CGRP). The results of immunohistochemical studies and peptide isolation and characterization have supported the prediction that CGRP is present in the central nervous system.

Calcitonin. The calcitonin injected intracerebroventricularly suppressed both gastric secretory volume and titratable acidity in rats. The effect is dose dependent (41 to 416 ng), long lasting and CNS mediated because parenteral doses 1,000 times higher are required to obtain an inhibitory effect. Calcitonin given intracerebroventricularly suppressed acid secretion stimulated by TRH, muscimol or insulin.[119]

That immunoreactive calcitonin messenger RNA and calcitonin are not detected in rat brain or pituitary[118] casts doubt on a possible CNS action of endogenous calcitonin. However, high-affinity binding sites for calcitonin have been localized in various brain areas by autoradiography.[120] More information on the endogenous ligand for calcitonin receptors in the brain is needed to clarify the significance of these observations.

Calcitonin gene-related peptide. The peptide injected intracisternally in urethane-anesthetized rats inhibited acid secretion stimulated by pentagastrin or histamine in doses ranging from 50 to 500 ng. In conscious pylorus-ligated rats, CGRP given intracisternally (1 to 10 μg) or into the lateral hypothalamus (4 μg) suppressed gastric acidity and secretory volume. Peptide action is reversed by vagotomy but not by adrenalectomy or chemical sympathectomy elicited with guanethidine.[121]

Neuropeptides That Influence Pepsin, Mucus or Gastrin Secretion

Neuropeptides that act within the brain to influence acid secretion seem also able to modify other secretory functions of the stomach (mucus, pepsin, bicarbonate and gastrin).

Bombesin given intracisternally increased the amount of mucus coating the gastric wall through CNS-mediated and adrenal-dependent mechanisms.[109] Indirect evidence indicates also that the peptide enhanced bicarbonate secretion. The release of gastrin associated with intracisternal administration of bombesin in rats depends on the integrity of the lateral hypothalamus and the sympathetic nervous system.[78] Intracisternal administration of TRH increased pepsin secretion whereas bombesin decreased it.[95]

Conclusions

Several of the neuropeptides uniquely stimulate or inhibit gastric secretion (Table 1). Methods used for studying interactions between brain and gastric functions have been based exclusively on electrical stimulation or lesions of various brain structures. Such an approach has generated conflicting data, without determining whether the variations were due to differences in species, stimulation variables, lesion size or a combination of these.[15] Neuropeptides appear as new standard probes and provide alternative chemical approaches to study brain-gut relations. Through their use, new insight has already been achieved on brain structures such as the paraventricular nucleus, so far neglected and shown to be sensitive to bombesin, CRF and CGRP-induced inhibition of gastric acid secretion. Neuropeptides seem useful tools not only to map brain structures but also to dissect the neurohumoral mechanisms involved in the central control of gastric secretion. Moreover, the high potency of these peptides to affect gastric secretion and their presence and that of their receptors in brain structures involved in regulating gastric secretion provide a neuroanatomic substrate for the concept that the described biologic actions of some of these peptides may have a physiologic relevance in health and disease.

Role of Gastric Motility in Experimentally Induced Gastric Ulceration

THOMAS GARRICK, MD:* Experimental investigations of gastric erosions have generally focused on the balance between aggressive and defensive processes in the stomach. The aggressive factors are acid and pepsin secretion, physical abra-

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sion of the mucosa by food and the effects of ulcerogenic agents such as ethanol, taurocholate and nonsteroidal anti-inflammatory agents. The protective factors include mucus secretion, blood flow, regeneration and restitution of gastric cells, bicarbonate secretion and the prostaglandins. Although various animal models of gastric erosions have been developed to study pathophysiologic processes in a controlled setting and in intact animals, relatively little has been done to evaluate the role of gastric contractions in producing gastric erosions. This may be due to the technical difficulty of monitoring gastric motility at the time of lesion formation.

One of the most frequently used experimental models of gastric erosion was first described by Selye[122] in 1936, who found that prolonged restraint of food-deprived rats resulted in the production of gastric erosions. Since that time many variations of this procedure have been studied to investigate, in a controlled setting, the various factors promoting and preventing such lesions; subjecting a fasted rat to restraint in a cold environment has been a reliable method for inducing them.[123] The lesions produced are hemorrhagic, occur only in the glandular portion of the stomach and do not generally penetrate into the muscularis mucosa. Many investigators have examined the effects of these procedures on acid output and other physiologic processes. The literature is sharply divided on the association of cold-restraint lesion formation and acid hypersecretion.[18,124,125] Acid hypersecretion has been thought by some investigators to be pathogenetic in lesion formation in this model system[125]; others have documented no effect or even suppression of acid secretion.[124] Lesions continue to form, albeit to a lesser degree, when gastric acid is neutralized during cold restraint.[126] The local application of acid solutions alone does not result in the formation of lesions.[127] However, experimental procedures that usually prevent cold-restraint lesion formation, such as vagotomy and administering anticholinergic agents (atropine), also drastically change gastric motility.

Altered gastric motility has more and more been implicated in lesion formation in experimentally induced gastric erosions. The evidence for this is, to a large degree, indirect. Infusing papaverine hydrochloride (an antispasmodic agent) suppresses lesion formation without suppressing acid secretion. Mucosal erosions have been reported after experimentally inducing gastric spasm by vagal or direct electrical stimulation[128]; these experiments, however, were done without monitoring acid secretion.

The most common methods of measuring gastric motility are indirect. Luminal pressure can be monitored using catheters passed into the stomach. Alternatively, electrical correlates of motility can be acquired using electrodes that have a suction cup on the tip to grasp the mucosa. In animals, gastric motility is typically monitored using a balloon surgically introduced into the stomach immediately before experimentation. The balloon is inflated and connected to a pressure-monitoring apparatus. Using such techniques, consistent increases in the amplitude and frequency of gastric contractions have been found in animals undergoing cold restraint. Vagotomy, administering anticholinergic agents such as atropine and inhibition of smooth muscle contraction by papaverine HCl reduce gastric hypermotility and lesion formation. One of the difficulties in analyzing these results is that the techniques of monitoring motility are insensitive, prone to serious artifacts and do not accurately monitor the actual motility of subsections of the stomach. More important, these techniques do not permit observation of normal processes such as feeding that also stimulate gastric contractions and acid secretion but do not lead to lesions in the stomach.

To correct these errors, gastric motility was monitored directly using surgically implanted strain-gauge transducers developed by Paul Bass, PhD, of the University of Wisconsin. These transducers are implanted in animals long term to avoid the artifacts of a recent operation and anesthesia; they do not seem to interfere with the normal functioning of the stomach and rats need not be restrained during monitoring.[129] These transducers have been used to compare the motility patterns found during unrestrained feeding with those occurring during cold restraint and lesion formation in the same rat. The contractile activity found in rats fasted for 24 hours is characterized by low-amplitude contractions occurring at a frequency of three to four per minute, occasionally interrupted by brief bursts of high-amplitude contractions. The onset of feeding is associated with unmistakable increases in the amplitude of gastric contractions. These contractions occur with a rhythmic frequency of four to five contractions per minute (Figure 10). During the several hours after feeding, the occurrence of high-amplitude contractions progressively decreases; the basic contractile frequency remains about the same. High-amplitude contractions in a normothermic animal last about ten seconds in both fasted and fed states.

When animals are again fasted, restrained by wrapping them in wire mesh and immersed to the xyphoid process of the sternum in water maintained at 20°C for three hours, gastric erosions uniformly develop. During this period, they become hypothermic and gastric hypercontractility occurs. Specific patterns of gastric motility distinguish cold-restraint-induced hypercontractility from food-induced hypercontractility. The amplitude of the contractions is usually the same during both states, but the frequency of the patterns is distinctly different. Whereas the frequency of contractions during most phases of the feeding cycle is three to five contractions per minute, during prolonged cold restraint it consistently drops below

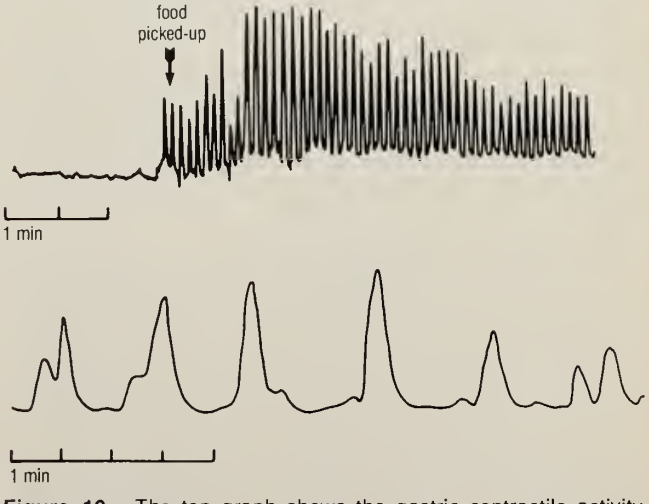

Figure 10.—The top graph shows the gastric contractile activity when a rat that has fasted for 24 hours starts to eat. The bottom reading shows gastric contractile activity when a 24-hour fasted rat is subjected to 3 hours of cold restraint at 20°C.

two contractions per minute. As the frequency of contractions drops, the average duration of high-amplitude contractions increases 200% to 400%, many contractions lasting 30 to 60 seconds (Figure 10).

Animals subjected to the same type of cold restraint were also prepared with gastric cannulas to monitor their acid secretory response. Uniformly, there was a gradual decrease in gastric acid secretion during the two hours of baseline and three hours of experimental conditions in control and experimental animals. The final acid secretory levels are significantly greater than zero and significantly less than baseline levels. Therefore, in this model, these procedures do not produce acid hypersecretion during lesion formation. However, the acid present may, as suggested by others,[127] still play a role in producing lesions. A pathophysiologic role for acid is evidenced by the definite decrease in lesion formation in animals treated with high-dose cimetidine or antacid solutions during cold restraint.[130]

The mechanism by which the described alteration in gastric motility results in mucosal lesions is not fully understood. Most of the evidence suggests that such contractions might result in a temporary restriction of blood flow to the mucosa, producing anoxic damage. The reduction of blood flow may be purely mechanical—tightly contracted muscularis constricts the small blood vessels traversing it. The restriction of blood flow might also involve vascular contraction or the shunting of blood away from the mucosa, thereby accentuating anoxic damage.[130,131] Postmortem examination of cold-stressed rats shows contracted stomachs with a blanched mucosa surrounding the erosions.[131] Such blanching is also seen during the formation of gastric erosions after vagal or local electrical stimulation.[128] Experimentally induced hemorrhage also results in mucosal lesions that closely resemble lesions after cold restraint. Cold-restraint lesions occurred only in the fundus of the stomach despite the fact that specific alterations in gastric contractility were also found in the antrum. This discrepancy may be accounted for on the basis of differences in blood flow: the antrum in both basal and stimulated conditions has a greater blood flow than does the corpus of the stomach.[132] Thus, fundic lesions may be more likely after such procedures than antral lesions.

In our experimental model, restraining animals in cold water produces gastric lesions without hypersecretion of acid. This procedure stimulates the onset of gastric contractions, the strength of which is comparable to those stimulated by food. However, the unusually prolonged duration of these contractions results in the stomach undergoing extended periods of contraction, which may play a role in the pathogenesis of mucosal erosions.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Radial Keratotomy

QUESTION:

Is radial keratotomy considered acceptable medical treatment for correction of myopia?

OPINION:

Although results from a carefully controlled, multicenter study indicate that radial keratotomy is a relatively safe and effective procedure for the correction of myopia in the short term, it is the opinion of the Scientific Advisory Panel on Ophthalmology that it should still be considered investigational. Results from the first year of the planned five year study, called the Prospective Evaluation of Radial Keratotomy (PERK), were made public in the fall of 1984.

It appears that radial keratotomy does have value for selected patients in reducing both myopia and dependence on the use of spectacles or contact lenses to correct that condition. However, the techniques of the procedure and its appropriate indications and contraindications are still evolving. Further, the procedure lacks an adequate level of predictability and, although small, there is some risk of permanent damage to the eye. Long-term results are unknown. The risks and complications should be detailed for all patients undergoing the procedure, particularly those whose motivation is purely cosmetic.

Until its long-term safety and effectiveness have been determined, therefore, this advisory panel feels that radial keratotomy should remain under investigation and should be done only with the approval and control of an institutional review committee.

Medical Staff Conference

Evaluating and Treating Intractable Cough

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and formerly Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *The topic will be "Evaluating and Treating Intractable Cough," a rather intriguing title, and Dr Michael Stulbarg will give this presentation. Dr Stulbarg is Adjunct Associate Professor of Medicine and Chief of the Chest Clinic here.*

DR STULBARG:† Thank you, Dr Smith, ladies and gentlemen. Many patients seek medical care for the complaint of cough. In 1979 about 13 million people saw their physicians for evaluation of cough and, in fact, cough was the second most common reason given for seeing a physician. Most of these coughs are self-limited, but in a few persons the coughs are persistent, worrisome and sometimes even disabling.

I would like to begin with the report of a case that we recently labored over for several months. I think this case emphasizes the complex and at times frustratingly prolonged evaluation necessary to achieve a specific diagnosis for a patient with intractable cough. I shall then turn to the physiology of cough, the complications of cough (because these are what often bring a patient to a physician's attention), the diagnostic approach to cough, including the long differential diagnosis, and finally to treatment.

Report of a Case

The patient, a 30-year-old housewife from Manteca (California), was referred because of chronic cough of three to four years' duration with worsening over the past year. The cough began insidiously during pregnancy and had persisted since that time. She noticed that it increased with exertion, but she could relate it to no other factors such as position, time of day or meals. She also complained of a chronic "tickle" in her throat possibly related to postnasal drip and of occasional ill-defined episodes of "choking" both day and night. She had been seen by several physicians who had given empiric trials of antibiotics and steroids with no benefit. Codeine gave considerable relief, preventing her posttussive emesis and reducing the disruption of her sleep.

Past history of pertinence included drainage of a right frontal sinusitis and nasal septoplasty. She said she had no allergies or occupational exposures. One sister had hay fever. Although review of systems elicited a variety of nonspecific complaints, the most intriguing symptom was that of occasional difficulty swallowing solids but not liquids.

On physical examination she was mildly obese and had an occasional dry cough. Vital signs were normal. There was no inflammation of either tympanic membrane and no hairs impinging upon them. There was no bogginess, erythema or polyps of the nose, and the oropharynx was without cobblestoning or visible mucus. The neck was free of masses and the trachea was freely mobile. Her lungs were clear to percussion and auscultation. On cardiac examination there were a palpable pulmonic component of the second heart sound and a grade 2/6 systolic ejection murmur.

Several studies had already been done, the results of which were unrevealing; these included a hemogram, chemistry panel, chest x-ray films, allergy skin testing, bronchoscopy, esophagoscopy and otolaryngologic consultation. Because her evaluation had been so detailed, I was concerned that she might have one of the uncommon causes of cough such as interstitial lung disease or, because of her cardiac findings, occult heart disease. Further workup included a new chest film, which was normal, pulmonary function studies, the results of which were normal except for high flow rates (a finding of questionable significance), and echocardiogram, which showed mitral valve prolapse with normal left ventricular function. A gallium lung scan, done in the search for occult interstitial lung disease, was minimally and probably insignificantly abnormal. To determine whether the patient might have airway hyperreactivity characteristic of asthma, a histamine challenge test was done and was within normal limits.

Because the results of these studies were unrevealing, she then underwent noninvasive exercise testing looking for clear-cut cardiac or pulmonary dysfunction. Oxygen uptake and minute ventilation were measured in response to incremental exercise. Results of the test showed greatly abnormal exercise tolerance for a 30-year-old woman, with abnormal ventilatory and cardiac responses. Repeat exercise testing with measurement of arterial blood gases and wasted ventilation was technically inadequate but did confirm the results of

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†Michael Stulbarg, MD, Adjunct Associate Professor of Medicine, and Chief of Chest Clinic.

(Stulbarg M: Evaluating and treating intractable cough—Medical Staff Conference, University of California, San Francisco. West J Med 1985 Aug; 143:223-228)

ABBREVIATIONS USED IN TEXT

CT = computed tomographic [scan]
FEV_1 = forced expiratory volume in one second

the prior study. Because of the unexplained abnormal findings on exercise testing, cardiologic consultation was sought and the clinical assessment showed no abnormalities. She then underwent cardiac catheterization. As the results were normal, I discharged her with the hope that she would feel reassured that we had done "everything." However, she called a few weeks later still distressed because of persistent coughing, especially at night. She was readmitted to hospital with the hope that the house staff would come up with something that I had missed. Her laboratory values and chest film were still normal. The house staff suggested the possibility of psychogenic cough. The psychiatrist who evaluated her felt that she was mildly depressed and that the cough could be due to a conversion reaction.

At this time the complaints of dysphagia and occasional substernal discomfort began to draw our attention. Because of these complaints, she was instructed to maintain the head of her bed at 30 degrees of elevation both day and night. This seemed to be associated with a decrease in her cough, suggesting the possibility of esophageal disease. A barium swallow study was therefore done and the findings suggested the presence of a mass impinging on the esophagus. However, a computed tomographic (CT) scan of the chest was normal. Because these studies did not exclude esophageal reflux or esophagitis, esophagoscopy was done. Results of the study showed that she did in fact have distal esophagitis and antritis. Treatment with antacids and cimetidine led to a pronounced improvement in her cough, but it was not until a few months later when metoclopramide hydrochloride was added to her regimen that her cough actually *disappeared.*

I apologize for presenting this case at such length, but I wanted to emphasize both the effort and the satisfaction of reaching a specific diagnosis.

Physiology of Cough

Cough may be a voluntary event or an unsuppressible reflex.[1-3] It may result from stimulation of irritant or rapidly adapting receptors by mucus or environmental irritants.[2] These receptors are present throughout the respiratory tract from the upper airway including the nose, sinuses, oropharynx and larynx to the lower airway including the trachea and the carinae, both the main carina and the more distal divisions or subcarinae.[1] Following stimulation of these receptors, there is a sudden inspiration, followed in turn by the compressive phase. This phase is marked by tightening of the chest and abdominal muscles against a closed glottis, with a rise in pleural pressure to between 100 and 300 mm of mercury.[4] At some point, not well defined, the glottis suddenly opens, allowing the rapid noisy exhalation we call a cough. Because of the high intrathoracic pressure that has developed, there is considerable narrowing of the proximal airways and very high linear velocities, resulting in more effective expulsion of mucus or foreign materials than is produced by simple exhalation. The dramatic decrease in the cross-sectional area of the trachea may result in linear velocities in excess of three quarters the speed of sound.[5]

Complications of Cough

It is often the complications of cough that bring a patient to medical attention. The devastating personal distress and social isolation sometimes produced by severe chronic cough are frequently unappreciated. Many patients restrict their social lives and refuse to go to restaurants, theaters or public gatherings because of the embarrassment they experience from their cough. Disruption of family life is a common complaint. The patient who first piqued my interest in chronic cough was a woman whom I was asked to see in the intensive care unit. She had nearly successfully killed herself on two separate occasions because of the impact of an unremitting cough on her marriage.

More common complications include sleep disruption; musculoskeletal, chest or abdominal wall pain; emesis, and syncope.[1,6-15] The mechanism of emesis is not clear, but it is thought to be related to irritation of the oropharynx. Syncope, a particularly dangerous complication of coughing, may be due either to the effect of increased pleural pressure transmitted directly to the cerebrospinal fluid or to the Valsalva-like effect of increased intrathoracic pressure on venous return and the resultant hypotension.[11-15] The mechanical stress of coughing may cause elevations of creatine phosphokinase levels[10] as well as result in fractures of ribs.[16] The cough-induced tearing of abdominal muscles may mimic a ruptured abdominal viscus, and on rare occasions patients have actually undergone an unnecessary operation.[6-9]

Less common complications of cough include pneumothorax, mediastinal emphysema, pneumoperitoneum[17] and headache.[18] Though poorly documented, other rare complications noted in the past have included fatigue, physical exhaustion, anorexia and rupture of subconjunctival nasal and anal veins.[19] In a recent report, bleeding from esophageal varices induced by coughing was documented.[20] Though rarely mentioned as a complication,[19] stress incontinence precipitated by coughing has been a not-uncommon reason for referral in our experience.

Diagnostic Approach

In approaching the differential diagnosis of cough, it may be helpful to consider the locations of cough receptors, because disease in any of these sites might elicit cough.[1] These receptors occur in the ears, the nose and sinuses, the oropharynx, particularly around the larynx, the trachea and the bifurcations of the large airways.[1,2] They do not occur in the periphery of the lung, perhaps explaining why some patients with extensive pneumonia have little or no cough until they begin producing enough mucus to stimulate the more proximal cough receptors. Receptors are also said to occur in the pericardium, the diaphragm and the stomach,[1] though these must be of much lesser importance as cough is not an important symptom of diseases in those organs.

The diseases that may affect these sites are many. In only two studies have the causes of cough been carefully examined (Table 1). One study, reported in 1981 by Irwin and coworkers, is a prospective study of 49 patients presenting to a chest clinic with unexplained cough in a one-year period.[21] All of these patients had been seen by at least one previous physician and had defied diagnosis for at least three weeks. They developed clinical criteria that included response to specific therapy for each of their diagnoses. The second

study, by Poe and colleagues, was a retrospective review of patients with prolonged coughing (at least two months).[22] Their study was based on a review of charts, and the criteria for diagnosis were not as clear as those in the first study.

Particularly impressive in both studies is the high frequency of asthma—38% overall (Table 1). This diagnosis required the finding of obstruction by spirometry or, if none was present, an abnormal response to bronchial challenge.[23] As abnormal bronchial reactivity alone is not sufficient for a diagnosis of clinical asthma, response to specific therapy was also required. Another large group, 21%, had postnasal drip, a somewhat controversial diagnosis.[24,25] Patients with this problem report the sensation of mucus "dripping" into the throat and the need for frequent clearing of the throat (as opposed to a deeper chest cough).[25] Alone, or combined with asthma, postnasal drip accounted for 35% of the cases of cough in the study by Irwin and associates. The nine patients given both diagnoses responded only partially to therapy for one, but completely to therapy for both diagnoses. In total, then, more than 50% of the patients presenting with intractable cough had either postnasal drip, asthma or both.

Another major category in the second study was postinfectious cough. Such patients were not included in the series by Irwin and co-workers, perhaps because most of them would not have been referred or would have been considered asthmatic. In fact, some did have positive response to methacholine stimulation, but we do not know if they responded to bronchodilator therapy. It has been shown that abnormal bronchial reactivity may commonly persist for as long as two months after a viral infection and then resolve without therapy.[26] Bronchitis occurred in 12% of the patients, almost always in smokers, and was usually associated with nonreversible airway obstruction. In all of the cases where information was available, cough was greatly improved or disappeared after cessation of smoking, as has been previously reported.[27]

Esophageal disease represented a small but important minority of cases. The case described would clearly have fallen into this group. This diagnosis required abnormal barium esophagograms, endoscopy showing esophagitis or abnormal results on pH monitoring of the distal esophagus. In the combined series only one patient had cough due to lymphangitic spread of cancer[21] and one patient was found to have an endobronchial adenocarcinoma.[22] Although cardiac disease was rarely the explanation for chronic cough, in one patient the results of a cardiac catheterization did show left ventricular failure.[21] Interstitial disease of the lung was the cause of cough in only one patient.[21] In the retrospective series they could not identify a specific diagnosis in 11 patients, of whom 7 were considered to be of psychogenic origin, though the criteria for this assignation were not described.[22]

TABLE 1.—*Causes of Persistent Cough*

Causes	Studies: Irwin et al, 1981[21] Patients	Studies: Poe et al, 1982[22] Patients	Total Patients	Total Percent*
Asthma	12	39	51	(32)
Postnasal drip	14	9	23	(15)
Asthma plus postnasal drip	9	..	9	(6)
Postinfectious	..	27	27	(17)
Bronchitis	6	13	19	(12)
Esophageal	5	4	9	(6)
Cancer	1	3	4	(3)
Cardiac	1	3	4	(3)
Interstitial disease	1	..	1	(1)
Psychogenic	..	7	7	(4)
Undetermined	..	4	4	(3)
Total	49	109	158	

*Percentage does not equal 100 due to rounding of numbers.

This list is by no means complete, but it does reflect the most commonly reported causes of cough. Presumably any disease of the lungs or airways may on occasion present with cough. Other unusual causes have been reported. Removing residual sutures from a prior resectional operation resolved cough in one group of five patients.[28] Stimulation of the tympanic membrane by hairs in the auditory canal has caused recurrent severe coughing paroxysms that resolve within several days of removing the hair.[29] Cases of radiologically occult bronchiectasis[30] or an endobronchial nematode[31] may present with chronic cough. Inhaling toxic substances may seem an obvious cause of cough,[32] but patients often deny their regular use of tobacco or marijuana. We have seen several patients whose coughs were due to causes not clearly described previously. Several patients have had cough associated with unexplained dryness of their oropharyngeal mucous membranes. Finally, we have seen one patient with a postoperative neuroma of the glossopharyngeal nerve resulting in a disabling cough elicited by any superficial stimulation of the neuroma, such as touch or inhaling cold air.

Medical History

Though many of these diagnoses seem straightforward, it is evident that patients with intractable cough would not have been referred to a specialty clinic for evaluation if that were so. Irwin and colleagues found that a specific diagnosis could be made by an appropriate history alone 80% of the time.[21] Several historical points are worth emphasizing.

Identifying precipitating causes or time of onset of cough may be particularly helpful. For example, patients with esophageal problems, heart failure or asthma are more likely to cough at night. Patients with bronchitis or postnasal drip may complain of cough and sputum production early in the mornings. A relationship to meals may suggest esophageal disease. Cough related to interstitial lung disease or asthma often increases with deep breathing or exertion. Identifying exposures to allergens or irritants both at home and at work may relate to cough. A prior history of infections may be important. Viral infections may cause persistent cough for as long as a couple of months following the episode.[26] Patients with severe chest infections as children may be more prone to pulmonary disease in adulthood. Bronchiectasis may be clinically silent (dry) for many years and then become symptomatic in adult life following a respiratory tract infection.

Some medications may cause cough. β-Blockers given orally for cardiovascular disease or topically for glaucoma may precipitate asthma. A variety of drugs including chemotherapeutic agents and nitrofurantoin may cause interstitial lung disease. Awareness of a prior response to empiric treatment may be very helpful. Such treatment may have been appropriate, but physicians are reluctant to continue treatment with either steroids or antibiotics without a specific diagnosis.

On review of systems, one should pay particular attention to the much-neglected nose and sinuses. Postnasal drip is an important cause of cough, and therapy is available.[24,25,32] Interpreting the complaint is sometimes difficult because so many patients complain of "sinus" problems,[32] but in those with troublesome cough aggressive treatment of this syndrome may be worthwhile. Airway symptoms are often not fully appreciated. Patients may belittle their chronic sputum production or consider it normal, but sputum production is an important symptom of either chronic bronchitis or chronic rhinitis. Dyspnea, if present, is an important clue to a wide variety of cardiopulmonary disorders. Symptoms of esophageal disease such as heartburn or dysphagia should be looked for specifically.[13] Knowledge of underlying diseases, such as Sjögren's syndrome, which could affect drying of the mucosa, for example, may be very helpful.

Physical Examination

A thorough physical examination is clearly necessary to separate the many diseases that may cause cough. Irwin and co-workers found it useful 60% of the time.[21] If a patient does not cough spontaneously, ask for a voluntary cough and listen to the quality of the cough. The cough is "wet" in patients with asthma, bronchitis and postnasal drip and "dry" in those with most of the other conditions. Note if it is a deep chest cough or just clearing of the throat and if it is brought on by respiratory tract maneuvers during the physical examination, such as laughing or deep breathing. On examination of the ears, look specifically for irritating hairs or impacted cerumen. Polyps or bogginess of the nasal mucosa and visible mucus or cobblestoning of the oropharynx (an accumulation of lymphoid tissue that is common in children, but not normally seen in adults) may suggest chronic rhinitis. Other important clues on physical examination would include neck masses or fixation of the trachea, unsuspected crackles or wheezes, cardiac murmurs or gallops, midepigastric tenderness, clubbing or any signs of systemic illness.

Other Studies

Although we rely a great deal on chest roentgenograms for diagnosis, patients with chest diseases may on occasion have perfectly normal chest roentgenograms.[33] Of patients with interstitial lung disease, as many as 16% may have normal chest x-ray films.[33] Endobronchial neoplasm, particularly bronchial adenomas, bronchiectasis, cystic fibrosis, endobronchial tuberculosis and especially foreign bodies may not be radiologically detectable.[33]

Our approach to diagnosis begins with a data base that includes history, physical examination, chest film and spirometry. At this point, I would like to focus on what to do when a diagnosis has not been made by this basic approach. If there is sputum, it may be worth examining.[34] The finding of eosinophils may suggest asthma, whereas the finding of abundant polymorphonuclear leukocytes and bacterial organisms may suggest chronic bronchitis.

Formal pulmonary function studies including measurement of diffusing capacity and maximal expiratory flow-volume loops may be more sensitive than simple spirometry for early diagnosis of interstitial lung disease, chronic obstructive pulmonary disease and upper airway disease.[25] Though not yet widely available, bronchial stimulation with histamine or methacholine is an important way of identifying abnormal irritability or reactivity of the airways, as occurs in asthma.[23] About a quarter of the cases in the series of Irwin and associates were diagnosed by this technique.[21] The test measures abnormal responsiveness of bronchial smooth muscle as assessed by the increase in airway resistance or the decrease in the forced expiratory volume in one second (FEV_1) following inhalation of methacholine or histamine. This is a dose-related phenomenon, and people with asthma respond to much lower doses of inhaled drug than do healthy persons. Unfortunately, the test is not perfectly discriminatory as some patients, such as those with allergic rhinitis, may fall into the so-called asthmatic range.[23] Corrao and associates reported the cases of a small group of patients with chronic cough who had no history of dyspnea or wheezing, normal findings on physical examination and normal resting pulmonary functions.[35] When tested with inhaled methacholine, they all had a decrease in their FEV_1, whereas none of the controls responded in that way to the same dose. All six of these patients responded to bronchodilator therapy with resolution of their cough. When the drug regimen was subsequently discontinued, the cough returned. This is the most convincing evidence of the cough variant of asthma.

All of the other diagnostic studies are of less common use, and the decision to use them is initially based on the history. A patient with severe persistent cough, such as the one presented here, eventually will undergo most of them. The other studies that were done in this patient including exercise study, gallium scan and CT scan are certainly of much lower yield and are rarely used in the workup of a coughing patient. Psychiatric evaluation has a clear role after extensive medical evaluation.[22] It is especially helpful in an adolescent with psychogenic or habitual cough.[36] We have seen two teenagers with this dramatic syndrome. Both were shy, had school-adjustment problems and in both cases the cough bothered the parents much more than it bothered the children. As reported previously,[35] the critical historical feature was that even though the cough occurred every few seconds during the day, making school attendance impossible, it disappeared with sleep. The cough increased when either nurses or physicians were present. In the first case, the parents unfortunately signed the patient out of hospital when we suggested that there might be a psychogenic cause. In the second case, the patient returned home with our reassurance and instructions to the parents simply to ignore the cough and reassure the child that all would be well. One week after returning home to Florida, upon awaking one morning, she said to her mother, "I don't think I need to cough anymore."

Treatment

Not every patient needs such an extensive workup. If the history is clearly suggestive, response to empiric treatment may be an adequate "test." Specific therapy for most of the diagnoses mentioned is straightforward. A notable exception is postnasal drip or chronic rhinitis. A combination of topical nasal steroids (beclomethasone dipropionate or flunisolide), combined with one of the long-acting antihistamine decongestant combinations, may be dramatically effective.[37] If the cause is clearly allergic, topical administration of a nasal solution of cromolyn sodium may be successful. Cough-

variant asthma may be resistant to simple dilators but a course of corticosteroids may be required.[21]

Irwin's group looked at both the immediate and long-term results of treatment.[21] At the time of follow-up 1½ years after diagnosis, 10% of patients were still coughing. All but one of these had refused to continue their medication as they were content to know the cause of their cough and did not want to take drugs. Only one patient, whose diagnosis had been postnasal drip, was considered a long-term treatment failure.

There is a great deal of interest in the nonspecific treatment of cough and, in fact, there are more than 100 cough preparations listed in the United States Pharmacopeia. Reassurance may be the most important treatment, though sometimes it is difficult to give until a fairly extensive workup has been completed. If patients do experience mucosal dryness, humidification or expectorants may play a role, but there is not a single study that shows a convincing role for either.[38] Nonetheless, like most clinicians, I use these medications on occasion in the hope of easing expectoration. Much interest has focused on antitussives,[39-42] but there is almost no role for their use in the treatment of chronic cough. However, during the period of recovery following a viral infection, or when a patient has a clear cause of cough for which there is no further treatment, such as radiation-induced fibrosis, they may be very helpful. Codeine in a dose of 30 to 60 mg every six to eight hours is still the apparent drug of choice, though all narcotics are effective.[42] Administering dextromethorphan, a nonprescription narcotic derivative, is also quite efficacious though probably less so than giving codeine. Occasionally a patient, such as one we recently saw with radiation pneumonitis, may respond dramatically to oral benzonatate (Tessalon), 100 mg, three to four times a day.

Lidocaine inhaled from a nebulizer is an innovative approach to the treatment of cough. Unfortunately, reports of treatment of only several patients with chronic persistent cough are available.[43-45] We have tried it in a few patients at a dose of 200 mg (5 ml of 4% lidocaine), lower than the recommended dose of 400 mg. We have seen only temporary relief of cough (up to 48 hours)—not the several-week response reported elsewhere.[43-45] Another innovative approach of possible value is that of "airway rest," analogous to bowel rest for colitis. With this approach one attempts to interrupt the cough cycle with bed rest, cough suppression and sedation. Though an attractive idea, it has not been formally tested.

Conclusion

In conclusion, cough is an extraordinarily common reason for physician visits. Most coughs are related either to viral infections and are self-limited or are smoking-related. However, cough may be a cardinal and even disabling symptom of many diseases. The cause of persistent cough can usually be found by careful, if sometimes exasperatingly protracted, evaluation. Treatment is most effective when given for a specific diagnosis. However, even after the most extensive evaluation, some coughs will remain undiagnosed. In such cases, reassurance and symptomatic treatment are vital.

Questions and Answers

HOMER BOUSHEY, MD: *I wonder whether it is really helpful to diagnose as asthma the combination of cough and increased bronchial reactivity. The main point of measuring airway responsiveness is to identify which patients with cough may obtain relief from antiasthmatic medications. As for the patient you presented, I would like to know your actual thoughts as to the cause of cough. Do you think there are cough receptors in the distal esophagus, or do you think she was actually aspirating gastric acid?*

DR STULBARG: I know you have been interested in the role of gastric reflux in the development of asthma in some patients, so I am glad you brought this up. According to some reports, this occurs by aspiration,[46] but actual documentation that that is what occurs is limited.[47] Since you are our resident expert on bronchial reactivity, I would like to throw the question back in your lap. How do you think cough occurs in patients with esophagitis?

DR BOUSHEY: *We have been interested in this problem for some time and have examined the possibility of a reflex causing bronchoconstriction in six patients who had both asthma and esophageal reflux and who reported that their asthma worsened when heartburn developed. We instilled saline or diluted hydrochloric acid into the distal esophagus and measured airway resistance. Neither solution had a measurable effect, even when the symptoms of heartburn were provoked. These negative results in a few subjects do not, of course, exclude the possibility of such a reflex, but my own suspicion is that small amounts of gastric material are being aspirated.*

DR STULBARG: In defense of the concept of recurrent aspiration in this case, this woman did give a history compatible with repeated bouts of aspiration. She recalled many episodes of choking, occurring day and night, sometimes awakening her from sleep.

WARREN GOLD, MD:* *The research group here that is interested in airway function has been able to show even in asthmatic subjects that specific stimuli may cause cough without causing contraction of airway smooth muscle. The emphasis in your presentation that cough may often be a manifestation of asthma ought perhaps to be modified. In fact, people who present with intractable cough but without other airway stimuli in the environment may be different from patients with typical asthma.*

DR STULBARG: I think you are referring to the excellent research that has been done here on cough by Dean Sheppard and associates. It is known that inhaling distilled water has a very potent irritating effect on people with asthma and, in fact, will cause both cough and bronchoconstriction. The group here has shown that cough and bronchoconstriction can be separated.[48,49] It has generally been believed that the reason asthma causes cough is that the bronchoconstriction causes deformation of the irritant receptors, resulting in cough. The work done here shows that that is not always the case. When subjects inhaled a bronchodilator before inhaling the distilled water, the bronchoconstriction but not the cough was prevented. In a separate study they showed that if subjects inhaled lidocaine before inhaling the distilled water, the cough but not the bronchoconstriction was prevented. So these studies showed very clearly the separation of cough and

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bronchoconstriction. How this relates to patients with cough and bronchial hyperreactivity, I am not sure.

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Epitomes
Important Advances in Clinical Medicine

Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in dermatology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Chloracne

CHLORACNE IS A DISORDER of sebaceous follicles characterized by the development of a profusion of open and closed comedones and small, straw-colored cysts. These lesions are heavily concentrated on the malar aspect of the face, the postauricular region, the axillae, the groin and the extremities. The finding of squamous metaplasia of sebaceous glands on histopathologic examination may aid in distinguishing this condition from other acneiform diseases.

Chloracne is caused by the ingestion, inhalation or transcutaneous penetration of certain halogenated aromatic hydrocarbons. The ability to cause chloracne appears to be highly correlated with the systemic toxicity of these compounds. For example, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin is an extremely toxic molecule and is also a potent chloracnegen. In contrast, 1,2,3,4-tetrachlorodibenzo-*p*-dioxin, an isomer that differs only in the position of two chlorine atoms, lacks the ability to induce chloracne and is relatively nontoxic.

The evidence that the presence of chloracne is the single best and most sensitive indicator of exposure to certain halogenated aromatic hydrocarbons comes from the investigation of accidental human contamination. The chloracnegenic compounds are often unwanted by-products of the synthesis of such substances as herbicides (2,4,5-trichlorophenoxyacetic acid, a major component of herbicide Orange) and wood preservatives (pentachlorophenol), or they may directly contaminate foodstuffs (polyhalogenated biphenyls).

Chloracne will develop within three to four months in those persons exposed to a sufficient amount of a chloracnegenic chemical and generally will resolve within two years. Chloracne may persist after exposure to the inciting chemical possibly due to release of these substances from fat reservoirs. In rare cases the condition can continue for as long as 30 years.

In conclusion, the development of chloracne is the single most sensitive indicator of exposure to certain toxic polyhalogenated hydrocarbons. These substances appear to be inescapable by-products of modern industrialized society.

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Recessive X-Linked Ichthyosis

RECESSIVE X-LINKED ICHTHYOSIS, an uncommon but not rare disorder, was clearly delineated from other genetic forms of ichthyosis through careful clinical and genealogic studies almost two decades ago. This form of ichthyosis is characterized clinically by the onset shortly after birth of closely adherent dark brown scales that most severely involve extensor surfaces of the extremities but also encroach on flexures. The trunk is involved as is the neck flexure; face, scalp, palms and soles are usually spared. Characteristic but asymptomatic opacities are present in Descemet's membrane of the cornea.

Although the prenatal syndrome of placental steroid sulfatase deficiency, characterized by extremely low maternal urinary estrogen levels despite fetal well-being, was first described in 1969, a decade elapsed before it was recognized that deficiency of this enzyme postnatally resulted in recessive X-linked ichthyosis. It has now been confirmed worldwide

that the microsomal enzyme, steroid sulfatase, is deficient in all patients with recessive X-linked ichthyosis.

Diagnosis of this disorder may be established by several methods. Prenatally, it can be inferred from a characteristic profile of maternal estrogen excretion and confirmed through direct enzyme assay in cultured fetal amniocytes. Postnatally, steroid sulfatase activity can be assayed in cultured fibroblasts or fresh leukocytes. The diagnosis can also be inferred from the accumulation of cholesterol sulfate, a substrate of the enzyme, in scale from these patients and in serum and erythrocyte membranes. In serum, cholesterol sulfate is carried on predominantly low-density lipoproteins (LDL); in cases of recessive X-linked ichthyosis, accumulation of cholesterol sulfate in LDL results in increased electronegativity of these particles—hence their altered electrophoretic mobility on lipoprotein electrophoresis. Thus, a readily available standard laboratory test may be used for the diagnosis of this disorder.

Other forms of ichthyosis have also been linked to abnormalities in epidermal lipid metabolism. This association is not surprising in view of the structure of stratum corneum, in which anucleated, keratinized corneocytes are surrounded by an extracellular matrix composed of neutral lipids (especially alkanes, triglycerides, free fatty acids, cholesterol and ceramides). Alterations in the composition of the extracellular lipid matrix affect the normal process of desquamation. Cholesterol sulfate, a highly amphipathic lipid, is one of the few remaining polar lipids in stratum corneum. Its hydrolytic enzyme, steroid sulfatase, also localizes to the intercellular regions of stratum corneum. Continuing hydrolysis of cholesterol sulfate as corneocytes move outward may be a critical factor leading to normal desquamation. In the stratum corneum of patients with recessive X-linked ichthyosis, absence of steroid sulfatase activity results in continued high levels of cholesterol sulfate, reduced levels of free sterol and impaired desquamation.

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Subsets of Systemic Lupus Erythematosus

NEWLY DEFINED SUBSETS of lupus erythematosus are of value in defining prognosis and suggesting management approaches.

Subacute cutaneous lupus erythematosus is a cutaneous lupus variant characterized by mild systemic disease and slow therapeutic response. The lesions may be annular and polycyclic or papulosquamous and psoriasiform. Areas involved usually are the shoulders, upper chest and back. There is little scarring, photosensitivity is common and patients usually have mild systemic disease. Serologic markers of subacute cutaneous lupus include HLA-DR3 and the antibody anti-Ro (SSA [Sjögren's syndrome antibody]). In patients whose diagnosis is a problem, skin biopsy for hematoxylin-eosin stain and immunopathology should be done. In addition to the usual lupus serologic tests, studies for anti-Ro (SSA) antibody and HLA-DR3 may help to define the problem. It is important to differentiate the psoriasiform type from psoriasis, as therapy for psoriasis—that is, ultraviolet light—is contraindicated in patients with lupus.

Neonatal lupus erythematosus is a subset in which patients may or may not have cutaneous lesions. A "raccoon rash" is most common, though discoid and subacute cutaneous lupus lesions also occur. Mothers of these children may have clinical or serologic features of connective tissue disease. Systemic features of neonatal lupus include congenital heart block, hepatosplenomegaly and failure to thrive. Antinuclear antibodies are usually found, and the anti-Ro (SSA) antibody seems to be a marker in the patients and their mothers. The anti-Ro (SSA) antibody may be useful in prenatal screening of mothers with connective tissue disease and in identifying neonates at high risk for the development of congenital heart block.

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Leukotrienes—Their Importance in Dermatology

THE LEUKOTRIENES CONSTITUTE a group of derivatives of arachidonic acid that were so named because they were first isolated from preparations of leukocytes and were all found to possess three conjugated double bonds. Neutrophils, macrophages, eosinophils, basophils and some populations of mast cells are capable of generating leukotrienes. Leukotrienes C_4, D_4 and E_4 (abbreviated LTC_4, LTD_4 and LTE_4) are unique among the known metabolites of arachidonic acid—which include the prostaglandins and thromboxanes—in respectively having the tripeptide glutathione, the dipeptide cysteinyl-glycine and cysteine alone, linked to the arachidonic acid skeleton. LTC_4 and LTD_4 constitute the major part of the activity that was previously called slow-reacting substance of anaphylaxis. In the skin, these two compounds cause increased permeability of postcapillary venules. Most significant, LTC_4 and LTD_4 are at least 1,000-fold more potent on a molar basis than is histamine. When injected into human skin, LTC_4 and LTD_4 produce classic urticaria, suggesting that these agents may be involved in the production of some types of urticaria, especially those that are unresponsive to antihistamine therapy. Unlike the prostaglandins and thromboxanes, the generation of leukotrienes is not suppressed by most nonsteroidal anti-inflammatory drugs such as aspirin, indomethacin or ibuprofen. However, corticosteroids do inhibit the generation of leukotrienes as well as the prostaglandins and thromboxanes.

Another leukotriene, designated LTB_4, which does not

incorporate a peptide or any amino acid into its structure, is an extremely potent chemoattractant for neutrophils. When placed on human skin, LTB_4 will induce the influx of neutrophils into the epidermis and dermis. Of clinical interest is the observation that there are elevated levels of LTB_4 in the lesions of psoriasis that are characterized in part by their dense infiltrate of neutrophils. Because the neutrophil is a rich source of LTB_4, it is as yet unclear whether the elevated levels of this leukotriene in psoriatic skin are purely the result of the presence of the neutrophils or whether the skin is itself generating this chemoattractant. In this context, it should be mentioned that another arachidonic acid metabolite called 12-hydroxyeicosatetraenoic acid (12-HETE) is generated by isolated epidermal cells, is 80-fold to 100-fold elevated in psoriatic lesions and, like LTB_4, can cause the influx of neutrophils into human skin. Thus, this agent may be initially responsible for attracting neutrophils into the psoriatic skin, and these neutrophils, through their release of LTB_4, then attract more neutrophils. Such proposed pathogenic mechanisms have yet to be clearly established. However, both the presence and the biologic potency of the leukotrienes in human skin provide very strong justification for research that will address the possible roles in cutaneous disease of these relatively recently isolated lipid and peptidolipid mediators.

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Bovine Injectable Collagen

BOVINE INJECTABLE COLLAGEN (Zyderm Collagen Implant) has been approved by the Food and Drug Administration as a xenogeneic device available for soft tissue augmentation. It is used to correct small distensible cosmetic defects such as disease- or trauma-induced atrophy, postcosmetic surgical abnormalities, shallow acne scars and age-related wrinkles. It is not appropriate, for example, for correcting ice-pick scars or facial hemiatrophy.

The material is produced from bovine dermis that has been subjected to pepsin hydrolysis to cleave the more antigeneic telopeptides and make its implantation more immunologically acceptable to the human host. The resultant product is dispersed in saline solution containing 0.3% lidocaine and is available in two concentrations: 35% by volume of collagen (Zyderm I) and 65% by volume (Zyderm II).

Treatment with injectable collagen requires an initial screening skin test. Approximately 0.1 ml of the material is placed intradermally in the volar area of the forearm and the site evaluated over one month. A positive test consists of redness, swelling or both after six hours and contraindicates treatment. About 3% of persons will have a positive skin test. Nevertheless, despite one negative skin test, 1.3% to 6.2% of patients will have treatment-associated reactions of swelling and redness at the treatment site. These treatment reactions usually last four to six months and occasionally longer. To reduce the possibility of these reactions a second skin test a month after the first can be administered in a cosmetically inconspicuous area of the face and the treatment begun two to four weeks after a negative second test. Also, if a patient has not been tested or treated within a 12-month period, it is advisable to retest once to reduce the possibility of a treatment reaction.

Correction of defects requires two to three treatment sessions at two- to four-week intervals. At these visits the Zyderm collagen is implanted in the superficial papillary dermis by serial punctures of the skin with syringes prefilled with the material. In implanting the substance, one must deliberately overcorrect and observe a blanching of the skin with wheal formation at the injection site. Correction with collagen is temporary and requires periodic maintenance at 6- to 12-month intervals.

Treatment reactions to collagen are, for the most part, cosmetic and consist of redness and swelling at the treatment sites; mild systemic symptoms are, rarely, associated with these reactions. The only serious sequela is one case—out of more than 100,000 treated persons—of unilateral loss of vision due to probable inadvertent intraarteriolar injection. Treatment-associated reactions are almost uniformly associated with anti-Zyderm antibodies that do not cross-react with human collagen. Though patients with collagen vascular disease are excluded from therapy, the fear that injectable collagen would induce collagen disease has been shown to be unfounded in its eight years of use.

Presently, studies are underway utilizing bovine injectable collagen in other than cosmetic areas such as cases of esophageal reflux, laryngeal paralysis, bone grafting, urinary incontinence and corns and calluses. A more robust form of collagen that is longer lasting and of value in larger cosmetic defects is being evaluated.

To date, the considerable experience with injectable collagen attests to its safety and efficacy. Nevertheless, only future studies will define its ultimate role in the cosmetic and noncosmetic medical armamentarium.

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The Diabetic Hand Syndrome

SEVERAL RECENT OBSERVATIONS SUGGEST that a thickened dermis and limited joint mobility of the fingers may be a common finding in patients with diabetes mellitus. Painful, stiff hands were described as an uncommon complication of insulin-dependent diabetes mellitus as early as 1957. Subsequent descriptions of this syndrome in 1978 and 1980 showed that this phenomenon is a rather common finding in children with diabetes mellitus. About a third of children with diabetes have been noted to have limited joint mobility of the hands and

a third of these have thickened skin on the dorsum of the fingers and hands. Most recently, it has been observed that limited joint mobility of the hands is also a common finding in adults who have diabetes mellitus.

Does this new finding have any significance in regard to other parameters of diabetes? Most reports suggest a correlation of these hand findings with diabetic retinopathy. It has also been suggested that this dermal thickening is the result of glycosylation of collagen, which results in a relative resistance of collagen to collagenase and a stiffer, stronger collagen. Increased glycosylation of collagen and the resulting changes in the biomechanical properties of this molecule occur normally with aging, and the occurrence in patients with diabetes is consistent with accelerated aging. Reports on the correlation of the diabetic hand with control of diabetes have, however, been conflicting.

In summary, skin and joint changes of the hands are fairly common findings in patients with diabetes mellitus. Along with other prognostic indicators, these changes should be sought on physical examination of diabetic patients. Although it is tantalizing to consider that hyperglycemia resulting in collagen glycosylation may be responsible for both dermal thickening and internal complications of diabetes mellitus, such a connection is far from proved. For clinicians today, the diabetic hand syndrome remains a relatively common and interesting finding that has a probable correlation with retinopathy.

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Malignant Melanoma—Recognition of New Histologic Variants With Favorable Prognosis

SINCE THE ORIGINAL WORK on ocular melanoma showed that patients with nonpigmented spindle cell melanomas have a better prognosis than those with other types, several studies have been done to determine which clinical and histologic variables have prognostic significance for primary cutaneous melanoma.

Results of these studies have uniformly indicated thickness to be a major prognostic indicator, but data regarding the significance of other histologic features remain less than clear, in part because of differences between studies and in part because some studies were based on the premise that lentigo maligna melanoma has a better prognosis than superficial spreading melanoma, which has a better prognosis than nodular melanoma. Therefore, cell types most often seen in patients with lentigo maligna melanoma were inferred to indicate a better prognosis.

In a recent study by Koh and co-workers, of 48 cases of lentigo maligna melanoma matched with non-lentigo maligna melanoma for site and thickness, a Cox multivariate analysis selected only thickness in predicting death. As with other large multicenter cooperative studies, this study indicated little or no independent impact of histologic features on the prognosis of patients with clinical stage I melanoma (primary melanoma with no clinical evidence of metastasis).

Histologically, lentigo maligna melanoma and superficial spreading melanoma are characterized by a radial growth phase or the horizontal spreading of malignant cells within and just beneath the epidermis (Breslow's level less than 0.76 mm or Clark's level I and II, indicating a good prognosis). In time, a vertical growth phase supervenes, expanding to more than 1.25 mm or Clark's level III, IV or V, indicating an increasingly worse prognosis. In nodular melanoma a vertically expanding nodule is characteristic and the radial growth phase may not be recognizable.

There is a histologic variant of malignant melanoma called minimal deviation melanoma that may prove to be the exception to the rule. This uncommon nevomelanocytic tumor appears clinically as a Spitz nevus, hemangioma or malignant melanoma. They occur on any body site, at any age and may arise in preexisting dermal nevi or in the midst of a congenital nevus. Histologically, cells making up an expansile nodule of the vertical growth component show mitotic figures but very minimal cytologic atypism such that, if the nodule arises in a nevus, differentiation of malignant from benign cells may be very difficult. When the nodule is located within Clark's level II, the lesion is called a borderline minimal deviation melanoma, borderline indicating the biologically benign nature of the lesion unless it penetrates to level III where its biologic behavior is unpredictable. (Other melanomas would predictably have a progressively worse prognosis).

Muhlbauer and colleagues recently reported a study of 21 patients with minimal deviation melanoma. The mean tumor thickness was 3.6 mm, or level V. After 57 months, only two of three deaths could be attributed to melanoma, the other patients being disease free.

Because of the less aggressive nature of these lesions, the authors express hesitation at assigning a Breslow or Clark's level because of therapeutic implications (local excision versus wide excision with possible lymph node dissection).

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A Micrographically Controlled Operation for Difficult Skin Cancers

ABOUT 40 YEARS AGO, Mohs developed a technique to remove skin cancers that has been modified to obtain a fresh tissue specimen for microscopic examination with careful mapping, now called micrographically controlled surgery.

Skin cancer accounts for 25% of all cancers in humans,

the most common of which are basal cell carcinomas that occur on sun-exposed areas of the head and neck. Persons with fair skin living in lower latitudes are at increased risk for the development of skin cancer. The incidence of skin cancer doubles for each 3°45′ of latitude toward the equator. Treatment includes curettage and electrodesiccation, excision, irradiation, cryosurgery and micrographically controlled surgical excision of tumors with high recurrence rates.

Technique

The micrographically controlled operation is done under local or regional anesthesia. The tumor is debulked. The specially angled saucerized tissue specimen is cut horizontally across the bottom in serial frozen sections. The entire undersurface and the epidermal margin of the excised tissue can be seen microscopically and mapped. One is then able to remove only tissue in which the tumor is microscopically persistent, allowing maximal preservation of normal skin. Mohs's surgical procedure is used for certain primary basal cell carcinomas and squamous cell carcinomas, most recurrent skin cancer, verrucous carcinoma and other paracutaneous neoplasms in the mouth and sinuses.

The criteria for selecting Mohs's procedure over other modalities in treating cases of primary basal cell carcinoma include tumor location, histologic analysis, size (greater than 2 cm) and clinical characteristics. In cases of recurrent basal cell carcinoma, a micrographically controlled surgical procedure is clearly the treatment of choice. The criteria are comparable for the less frequently occurring squamous cell carcinomas.

Tumor location is important. Areas of high recurrence are embryonic planes including the nasal septum, the nasal ala, the junction of the nasal ala with the nasolabial fold, the periorbital region and the periauricular region extending to the temple. Basal cell carcinoma follows the paths of least resistance, along facial planes, periosteum, perichondrium and eyelid tarsal plate, spreading along these structures before invading.

Primary basal cell carcinomas have several histopathologic characteristics with differing biologic behavior. Morpheaform or sclerotic basal cell carcinomas, multicentric infiltrating tumor or the keratinizing aggressive basal cell carcinoma (metatypical carcinoma) can be clinically aggressive with higher recurrence rates than nodular basal cell carcinomas. Sclerotic basal cell carcinoma can have a large subclinical extension, especially on the temple and forehead.

A third factor is tumor size. For tumors larger than 2 cm, Mohs's operation is generally recommended. The cure rate for Mohs's procedure is 98.6% for tumors between 2 cm and 3 cm in diameter and 90% for tumors greater than 3 cm in diameter. Most basal cell carcinomas are well-defined nodules. However, some have ill-defined clinical borders exhibiting a multicentric nature. In this situation Mohs's operation might be considered a treatment of choice if a large, clinically judged excision is not appropriate.

Incompletely excised basal cell carcinomas have variable recurrence rates: 82% on eyes, ears and nose and 25% on the remainder of the head and neck. Mohs's surgical procedure has a success rate of about 96% for recurrent basal cell carcinomas compared with the 50% success rate of other modalities. It has the additional advantage of preserving the maximal amount of normal skin.

In conclusion, location, histologic characteristics, size and clinical nature of a primary skin cancer are important in deciding the most effective treatment modality.

New techniques to improve the cure rate are immunofluorescent and immunoperoxidase staining antibodies to keratin. This keratin antibody staining in frozen section appears to be an effective method of distinguishing strands of cancer cells in poorly differentiated squamous cell carcinoma or morpheaform basal cell carcinoma from inflammatory cells.

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Minoxidil

MINOXIDIL IS a potent peripheral vasodilator used in treating patients with hypertension. When taken orally, the drug causes a reversible, nonvirilizing hypertrichosis in most patients. In women, the increased hair growth involves the face, shoulders and limbs and, in men, there is a generalized increase of body hair.

Topical minoxidil, not yet approved by the Food and Drug Administration, is being studied in large, multicenter projects to assess the drug's efficacy and safety when applied to the scalp of patients with alopecia areata and those with androgenetic alopecia.

In men, women and children with alopecia areata affecting 25% to 99% of the scalp, topical application of minoxidil produces hair growth in about 30% of the patients after a year of treatment. The results with 1% and 3% topical minoxidil are similar. After two and three years of topical treatment, it is possible that a higher percentage of patients, including some with 100% scalp hair loss, will grow cosmetically acceptable hair. One study has shown a substantially greater response rate using 5% minoxidil in cases of alopecia areata.

In men with androgenetic alopecia, cosmetically acceptable hair growth is achieved in about 30% after twice-a-day application of minoxidil for one year. Both 2% and 3% topical minoxidil produces similar results in patients with androgenetic alopecia. Hair growth begins after four to six months of treatment. The presence of pigmented hairs longer than 1 cm is a favorable indicator for response; the greater the density of such miniaturized hairs, the more likely the patient will respond well to topical application of minoxidil. In addition, the shorter the duration of the balding process and the smaller the balding area, the better the likelihood of a cosmetically acceptable response.

Topical minoxidil appears to be safe in those with a normal cardiovascular state. Side effects have consisted mainly of mild skin irritation in only a few patients.

The mechanism by which minoxidil stimulates hair growth in patients with alopecia areata and androgenetic alopecia is unknown and it is the first drug to grow hair in both of these unrelated conditions. Many questions remain to be answered. The optimal concentration, the frequency of application and the duration of therapy all must still be determined.

Topical minoxidil is a promising new drug for stimulating hair growth in patients with alopecia areata and androgenetic alopecia. Those using it must understand that it works very slowly, treatment is necessary for at least one to three years, perhaps longer, and the hair regrowth may not persist after treatment is stopped.

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Editorials

WJM Welcomes Arizona and Montana

The Arizona Medical Association and the Montana Medical Association have each voted to join the *WJM* family of sponsoring state medical societies. They join the medical associations of California, Idaho, Nevada, New Mexico, Utah, Washington and Wyoming (as well as six research and specialty societies) in designating *WJM* as their official scientific journal. The editors and staff of *WJM* welcome them and look forward to many years of shared endeavor.

The monthly circulation of *WJM* will now be something more than 53,000. It is worth noting that the subscribers and readers extend far beyond the boundaries of the western medical associations and societies that officially sponsor the journal. There are paid subscribers in every state of the union and most foreign countries. Reprint requests during the last year for the Epitomes section alone (the only section for which we are able to monitor this) have been received from Australia, Belgium, Bulgaria, Canada, Cuba, Czechoslovakia, East Germany, Ecuador, Estonia, France, Israel, Italy, Mexico, Nigeria, Poland, Romania, Spain, Venezuela and West Germany.

So it is clear that as the journal has been developing its strong base among the western states, it has not only been serving the members of its family of state medical associations and other affiliated societies, but has also begun to extend the influence of medicine in the West to the rest of the nation and to many far away parts of the world.

MSMW

The Mind, the Brain and Ulcer Disease

Peptic ulcer disease in humans results from an imbalance between aggressive forces—acid and the proteolytic enzyme pepsin—and the endogenous defense mechanisms, which may include mucus and bicarbonate secretion, the maintenance of adequate mucosal blood flow and the inherent ability of the epithelium to maintain its integrity in the face of a large proton gradient. Since the range of acid-pepsin secretion is wide and most duodenal ulcer patients fall within the normal limits, the implication is that impaired mucosal resistance is the primary factor in ulcer formation. These defensive mechanisms are apparently influenced by both genetic and environmental factors, but quantitative assessment of these factors is not yet possible.

To perceive disease formation as the result of a simple imbalance of two opposing forces is of course reasonable, but simplistic. It would be equally simplistic to assume that an interruption of an intercontinental telephone conversation occurred because the plug was pulled on one of the telephones involved. Although it may be the case, the problem may well exist anywhere in the myriad of switches and computers that permit the conversation to occur.

In the symposium "Neurobiologic and Psychobiologic Mechanisms in Gastric Function and Ulceration" published in this issue of the journal, a group of scientists representing multiple disciplines review the data available on this subject. Although the symposium is scholarly in its scope, one is left with a sense of confusion, not from the presentation specifically, but from the unease one senses when confronted with many pieces of a gigantic, complex puzzle not yet organized.

Several questions contribute to this complexity. Are these experimental animal models relevant to human function and disease? Can the interspecies variations (cat, dog, rat) be reduced sufficiently to permit adequate conclusions? Can any of the numerous mechanisms noted in the symposium—the neural pathways, mechanoreceptors, chemoreceptors, osmoreceptors in the gastrointestinal tract and the liver and neuropeptides in the brain and gut—be shown to be physiologically relevant and not just demonstrable phenomena elicited in the experimental setting? Furthermore, to fully understand the mechanisms that control both feeding behavior and gastric function in humans, should we not search for the integrative links among (1) experience, that which occurs from the environment; (2) internal conflict—that is, unconscious processes of the mind—and (3) the neurophysiology?

As the discussants describe, the amygdalar structure within the limbic system has been implicated in emotionality and responsivity to stress. Neural connections between the central nucleus of the amygdala and the lateral hypothalamic area have been documented in rats.[1] Electrolytic lesions of the centromedial amygdaloid area result in marked alteration of gastric acid secretion. The lateral hypothalamus has, in addition to its connections with the limbic system, connections with the autonomic nervous system. The nature of these connections, however, is still unclear. The lateral hypothalamic area in various species has been shown to be clearly involved in the regulation of gastrointestinal function. Therefore, the evidence suggests that there is demonstrable "machinery" that may control gastrointestinal function existing well within the physical confines of the brain. In addition, in the symposium, Novin states that there "seems to be good evidence that the entire upper alimentary canal, the liver and the brain provide input important in feeding regulation." However, he goes on, "none are necessary components of that regulation," strongly suggesting "a redundant system of multiple inputs." Presumably, the brain integrates the diverse information "in a hierarchical organization," with increasingly complex afferent input and integration probably requiring higher levels of the nervous system.

However, it is not yet established how the *mind*—the anatomically elusive mental apparatus that is the source of both conscious and unconscious psychic processes—interacts with the physical system described in the symposium. What is the role of the mind in regard to gastric function and ulcer formation? There is some evidence that the mind does influence the rate of acid secretion and the motility of the stomach, but it is not yet established that this relationship is important in the cause of ulcer disease. Psychological stress has been considered to have an important role in either the genesis or exacerbation of ulcer disease. Here again, the evidence has been

suggestive but inconclusive.[2] A recent report about two men who experienced extraordinarily stressful life events lends support to the hypothesis that psychological strain can result in actual ulcer disease.[3] Ulcer symptoms in one began soon after he experienced the death of six family members in a six-week period and feared his own death. In the second case, symptoms followed his being accused of grand theft, being under police surveillance and losing his job. Both patients had greatly increased gastric acid secretion rates that decreased to normal after admission to hospital and reassurance in the first case and acquittal in the second. But by what mechanisms do these and other experiences translate into disease?

The literature on the subject since the 1930s has concentrated on the presence of excessive dependency needs in patients with duodenal ulcer disease, and recent preliminary data, in fact, suggest that peptic ulcer disease patients are more dependent than age-matched control subjects.[4] Following psychoanalytic theory and data from unconscious material obtained from ulcer patients given the Thematic Apperception Test, one might suggest the following: the young infant, perhaps genetically vulnerable, experiences real or fantasized loss, perceived as the absence of or inadequate fulfillment of the need to be soothed via adequate feeding. The wish to be fed is associated with a cephalic phase response of gastric acid secretion. Later in life, this adult who has become excessively dependent suffers a real or threatened loss, reacts with a sense of helplessness and regresses to the "oral phase" where the association between loss and acid secretion occurs. However tempting this scenario might be, it must be noted that it still does not pinpoint the elusive link between the psychological process and the brain function discussed in the symposium. Furthermore, the fact that ulcer disease may be caused or exacerbated by such a dependency "trait" does not necessarily imply that adults with the trait are automatically predisposed to peptic ulcer disease. In view of the recent recognition of the concept of heterogeneity in medical disorders, especially clear in peptic ulcer disease, it is no longer necessary to explain all cases of any disease with the same pathophysiologic description.[5] Therefore, it is theoretically possible that psychological factors may be relevant in one subgroup and not in another. There may be many routes to the eventual hole in the gastroduodenal mucosa, and our puzzle remains unsolved with only a few scattered links here and there.

Sigmund Freud apparently thought that this search to discover a specific neurochemical link between psyche and soma was a fruitless venture. In the last account of his ideas, Freud acknowledges the presence of both the bodily organ (the brain) and the mental apparatus with its conscious and unconscious components (the mind). Regarding the interaction of mind and brain, he wrote, "Everything that lies between is unkown to us, and the data do not include any direct relation between these two terminal points of our knowledge."[6]

Although the void in our understanding of the mind and brain has seemed unbridgeable, one must wonder if new diagnostic techniques such as positron-emission tomography will elucidate cortical functions not yet appreciated[7] or whether we will continue to label and identify parts without understanding their true relationships.

These problematic questions and the enormous data pool already accumulated should not discourage us, but rather, as so often seems the case in scientific investigation, act as a catalyst for more specific questions that will permit clarification and hopefully a substantial furthering of our knowledge.

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Biological and Societal Interdependence

IF ONE READS CAREFULLY the specialty conference on gastric function and ulceration that appears elsewhere in this issue, one is impressed by the as yet poorly understood interrelationships and indeed interdependence among the biologic processes discussed. If one has been a more or less regular reader of these columns, one may have noted that this writer has often reflected on the poorly understood relationships and indeed interdependence among the social, economic and political pressures in today's very human and very technologic society. And a reader may also have discerned that this writer sees a link between biological and societal interdependence with biologic connotations that are also as yet poorly understood.

In both biology (whether human or not) and human society one senses dynamic and ever-changing relationships where many things are going on at once, each affecting and being affected by all the others. Deductive science with its linear approach, in which most of us have been trained, does not now seem adequate to deal with the merging dimensions of biological and societal interdependence. New methods and new approaches should be sought. If these can be developed in biology and human medicine, then medicine could become the basic biologic and social science to develop a better understanding of the human and societal interdependence which is so much a reality in the world today. This could be a major challenge of the times.

MSMW

Water Distribution and Oxygen Delivery

. . . Too much water hast thou, poor Ophelia.

WILLIAM SHAKESPEARE
Hamlet

WATER HAS DEFINED geographic boundaries and separated national and cultural groups throughout the ages; moreover, water rights have been a source of endless human conflict. It is not surprising, therefore, that strongly held views on the problems of body water distribution and fluid management have separated physicians and, indeed, the various medical specialties. Internists most often are confronted with edema-

tous patients in cardiac, renal and respiratory failure; to a large extent, these patients require diuretics with water and salt restriction. On the other hand, surgeons who should know more about shock from having caused much of it are alleged to flood their patients with too much salt and water. Elsewhere in this issue, Waxman and associates have critically reviewed the problems of fluid therapy with blood and plasma substitutes, emphasizing oxygen transport properties. They wisely dismiss crystalloid solutions which, though cheap, are inefficient plasma expanders because they are preponderantly distributed in the interstitial space; only a relatively small proportion (less than 20%) is left in the plasma volume at the end of the infusion and this subsequently disappears from the plasma volume exponentially.[1]

A major neglected problem is the pronounced redistribution of water that commonly occurs with shock, trauma and critical illness, namely, expanded interstitial water in spite of hypovolemia.[2] This occurs despite the frequent claims of the crystalloid proponents that if you give enough crystalloids, the plasma volume eventually will be restored. To do this, Lucas and colleagues[3,4] give 30,000 ml more of fluids than are lost in the urine and they require a 25-kg weight gain; they found an exceedingly high percentage of their resuscitated patients required digitalis. This position is somewhat reminiscent of the used-car salesman who claimed he lost money on every sale, but made up for it by the volume, or of Hamlet who discovered his beloved face down in the brook.

Waxman and co-workers expertly summarize the physical properties of dextran, hydroxyethyl starch, perfluorochemicals and stroma-free hemoglobin. The latter is not approved by the Food and Drug Administration (FDA), and Fluosol DA, which was the only perfluorochemical that underwent FDA testing, was withdrawn after unsuccessful clinical trials. These investigators have evaluated the physical capacities of the two new agents that are of great theoretical interest because they are able to bind and carry oxygen, even though they are not yet clinically available. Administration of 1,000 ml of Fluosol DA 20% increases the arterial oxygen content 2.3 ml per dl in cases of severe anemia.[5] This is equivalent to the amount produced by about 1½ units of packed erythrocytes.

Possibly of greater usefulness than the physical properties of presently unavailable agents are the physiologic capacities of presently available agents to affect oxygen transport and metabolism in a disturbed circulation. The oxygen content of arterial blood in vitro is less important than oxygen delivery to the tissues in vivo because agents that draw more water into the plasma volume increase proportionately the cardiac output and may deliver more oxygen than the agent that merely contains more oxygen. It might be more appropriate to describe the immediate direct physiologic effects of whole blood transfusion or its components—packed erythrocytes, albumin and plasma protein fractions.[5-9] This is necessary to develop a "gold standard" with natural fluids against which the relative efficacy of various synthetic agents may be assessed under various clinical circumstances. Available data show that (1) in normal preillness conditions one unit of whole blood produces small but significant increases in cardiac index and oxygen delivery but little or no improvement in oxygen consumption; (2) in postoperative conditions, one unit of whole blood increases cardiac index an average of 0.44 $\pm$ 0.10 (standard error of the mean) liters per minute per m^2 mean arterial pressure 9 $\pm$ 3 mm of mercury, comparable increases in the derived hemodynamic variables, oxygen delivery of 87 $\pm$ 27 ml per minute per m^2 and oxygen consumption of 24 $\pm$ 8 ml per minute per m^2; (3) in patients with early postoperative shock, acute respiratory failure and sepsis, administering 500 ml of whole blood or plasma expanders produces greater increases in cardiac index, oxygen delivery and oxygen consumption than under normal preoperative control conditions; (4) in general, administering 250 ml or 500 ml of plasma expanders produces greater hemodynamic and oxygen transport effects than does giving 1,000 ml of saline, and (5) in the terminal state there is very little improvement in any of the hemodynamic and oxygen transport variables after transfusions of plasma expanders.[5-10] Thus, in the early stages of shock and critical illness, the various natural and synthetic colloids expand the plasma volume more than the infused volume,[1,9] but in the late stages of shock, capillary leak or maldistribution of body water (or both) limits their effectiveness.[1]

Matsuda and co-workers[6] observed that the physiologic responses of administering 500 ml of dextran 40 varied widely depending on the underlying state of the patient. Similarly, McCartney and Appel compared the relative effectiveness of the use of hydroxyethyl starch in normal persons, patients before, during and after an operation, patients with sepsis, elderly persons, patients with cirrhosis and those with respiratory failure (S. F. McCartney, MD, and P. L. Appel, MPA, written communication, February 1984). In essence, the physiologic effects of blood, plasma components and synthetic plasma expanders are dependent on the blood volume deficit, the peripheral circulatory defect, the etiologic basis of the disturbed circulation, the duration of the shock state and the reserve capacity of the heart, lungs and other organs.

The therapeutic objective in a critically ill patient is not to restore cardiac function to a normal state but rather to restore the oxygen transport functions of the circulation to their optimal values defined empirically by the values of survivors of life-threatening critical illness, because these values are related to, and may indeed be determinants of, survival.[11] To accomplish this it is necessary to mix and match the physiologic defects that a patient has with the physiologic effects of available therapeutic agents. This is not properly done on theoretical grounds based on in vitro physical properties, but by empirical in vivo measurements of the relative physiologic effectiveness of each of the various agents under each of the various clinical conditions. In essence, the empirical trial of therapy under specific conditions as advocated by Hippocrates provides objective evidence for clinical decision making. An agent is not necessarily inherently good or bad, but rather more or less appropriate than another agent according to its physiologic effects in a given clinical condition.

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The Importance of Caring

MUCH IS BEING WRITTEN these days, and much is being said, about the caring function of physicians. It well may be that where there is this much smoke there may be some fire. Perhaps it is time for physicians and the profession as a whole to devote more time and attention to the caring part of patient care. There is reason to believe that too often this may be something taken for granted by physicians, but not so much so by patients or by society. In fact there already may be some significant social, economic and political fallout from the perception that physicians and the profession are caring less—or the reality of it.

Caring is a very human and very personal matter. It is not particularly scientific although science and technology can be used as tools for caring. One can care for things—a well-restored vintage automobile, for example—but in medicine and medical practice the caring must be for patients and for the health and well-being of people. To be effective, caring must be communicated and come across to a patient or to the public as something genuine and comforting—something that can engender trust. When developed and used effectively—that is, communicated—caring can become a powerful therapeutic tool for a practicing physician and, perhaps surprisingly, an effective political tool for the medical profession. Nobody wants a doctor or a health care system or a medical profession that doesn't care.

Yet there is evidence that caring is not now the powerful force that it has been and can be in medicine. The beloved horse-and-buggy doctor cared and gave solace and comfort. True, there often was not much else he could do, but the caring was appreciated and society thought well of the horse-and-buggy doctor. Now physicians can do more with modern science and technology than has ever before been possible, and many are so fascinated by this that they become so preoccupied by the scientific diagnosis and the scientific treatment of a disease that they seem too often to neglect the care and treatment of the very human person who has the disease. The human caring communication between doctor and patient or between the medical profession and society is apt to receive short shrift, or is simply overlooked entirely. Nor has the compartmentalization of medicine into specialties and subspecialties done much to help, since a result has been compartmentalization in patient care and, therefore, less emphasis on the less scientific needs of the whole person who may be affected in many ways by the trouble in one or more of his or her compartmentalized parts. And now, what is left of caring seems to be threatened by new pressures in health care that are beginning to drive significant economic wedges between doctors and patients, wedges that some think will surely erode and perhaps finally altogether destroy a physician's incentive for caring.

There is already evidence of economic and political fallout from these trends which seem to have been accelerating so rapidly in recent years. Many patients have begun to sense that the care of physicians is less than satisfying to them and have sought care (and caring) elsewhere. This clearly has had and is having economic impact on physicians. And in the political arena there is mounting evidence of significant progress by other health care professionals to extend their scope of practice in response to what is perceived as a growing demand for their services. There has been surprisingly little interest among practicing physicians or in the medical profession as a whole either in identifying the cause or effecting a cure for what already seems to be a serious ailment in modern medicine and modern medical practice.

But perhaps it is not too late. There are soon to be many more physicians and many of them will have more time on their hands, time that it will be to their economic advantage to use for caring and communicating—with patients and the public. And it is not to be forgotten that the desire to care for people, as well as their ailments, is why most physicians decided to become doctors in the first place. What is needed now is for practicing physicians and the medical profession to resurrect the human and caring aspects of their great calling, bring them to the fore, and make medical science and technology, and the social, economic and political forces that are so evident today, their servants in this cause and not let them be the masters. This can and should now become a personal commitment of every physician and an organizational commitment of the profession. It may well be that the power inherent in the caring function can serve physicians as well now as it has in the past. After all, the real and ultimate social, economic and political power in this nation still lies in the hands of the people—people who nearly all will somehow have their lives affected by physicians.

MSMW

Case Reports

Pseudofractures in Patients With Low-Turnover Osteoporosis

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PSEUDOFRACTURES (Looser's zones, Milkman's fractures) were first described in Germany and Austria in the period immediately following World War I.[1-3] Their cause was considered to be lack of adequate nutrition (hunger osteopathy) and many of the cases initially reported to have this radiographic finding had evidence of osteomalacia or rickets. In 1930 Milkman described the first case of pseudofractures in the English literature.[4] They are characteristically linear, radiolucent areas, frequently with sclerotic margins, that most commonly occur perpendicular to the periosteal surface in ribs, scapulae, the pelvis and long bones. Their presence has proved to be a useful roentgenographic sign of osteomalacia. In fact, recent reviews of osteomalacia have emphasized the diagnostic value of pseudofractures and have reasserted that pseudofractures are a pathognomonic sign of that disorder.[5,6] We report, however, two patients in whom multiple, symmetric pseudofractures occurred in the presence of low-turnover osteoporosis and in the absence of any evidence of osteomalacia.

Reports of Cases

Case 1

The patient, a 73-year-old woman, was referred to the Bone and Mineral Clinic at The Oregon Health Sciences University for evaluation of osteopenia presumed to be due to osteomalacia. A year earlier she had the onset of sharp or aching bilateral inguinal pain that was considerably worsened with weight bearing or hip movement. After several months of gradually increasing discomfort, she sought treatment from a chiropractor who "manipulated" her pelvis. These manipulations were carried out periodically over a six-month period but the discomfort continued and she was finally confined to a wheelchair. She saw a physician and a radiograph showed pseudofractures in all four pelvic rami (Figure 1). A technetium Tc 99m diphosphonate bone scan showed increased uptake in those areas but was otherwise unremarkable.

The patient said she had had no previous bone disease, rickets, bone tenderness, back pain, diarrhea, weight loss, operations, alcohol use or renal disease. The patient's only medications were six tablespoons per day of Maalox or Mylanta for esophageal reflux (two years) and one multivitamin per day that contained 400 IU of ergocalciferol (two months). She had received a two-month course of estrogen therapy that had been discontinued five years before.

On physical examination she was mildly obese and had mild dorsal kyphosis without vertebral tenderness or scoliosis. There was minimal tibial and clavicular tenderness and slight generalized weakness. An initial laboratory evaluation elicited the following values: serum creatinine, 1.0, calcium, 9.6, and phosphorus, 3.5 mg per dl; total protein, 7.4 grams per dl; alkaline phosphatase, 118 mU per ml (normal, 35 to 105). Serum aspartate aminotransferase (AST, formerly glutamic-oxaloacetic transaminase) and bilirubin concentrations were normal. Serum 25-hydroxycholecalciferol level was 36 ng per ml (normal, 10 to 50) and serum 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D_3) concentration was 53 pg per ml (normal 30 to 75). Fasting urinary adenosine 3′:5′-cyclic phosphate concentration was 3.4 nmol per dl glomerular filtration rate (normal, 1.8 to 4.5) and 24-hour urine calcium excretion was 114 mg while on a routine diet.

Radiographs of the lumbosacral spine showed osteopenia with anterior wedge fractures of L-2 and L-3. Single-photon absorptiometry done at the junction of the distal and middle thirds of the radius showed a bone mineral content of 0.64 grams, bone width of 1.2 cm and bone mineral content/bone width of 0.53 grams per cm^2 (normal for age and sex, 0.57 ± 0.085 standard deviation [SD]). At the distal radial site (2 cm proximal to the ulnar styloid), the bone mineral content was 0.7 grams, bone width 2.5 cm and bone mineral content/bone width 0.28 grams per cm^2 (normal, 0.4 ± 0.103 [SD]).

A percutaneous trephine bone biopsy was done and an 8-mm specimen obtained from the iliac crest after tetracycline labeling; it was processed by nondecalcifying methods,[7] sectioned and stained for histomorphometric analysis (Robert Recker, MD, Creighton University, Omaha, Neb) (Table 1). The trabecular bone volume was greatly depressed (6%) and both static and dynamic measures of bone remodeling were

TABLE 1.—*Histomorphometric Features of Two Cases of Pseudofracture*

	Case 1	Case 2	Normal
Trabecular bone volume, cu mm	0.066	0.043	0.148 ± 0.033*
Osteoid volume, mm	....	....	0.0034 ± 0.0024*
Osteoid seam width, cu mm	0.0059	0.0065	0.00639 ± 0.00072*
Fractional osteoid surface, %	0.115	0.14	0.121 ± 0.075*
Fractional double-labeled surface, %	0.0066	....	0.123 ± 0.015*
Fractional resorption surface, %	0.0297	0.0617	0.039 ± 0.009*
Mineralization lag time, yr (range)	0.618	....	0.0575 (0.023-0.143)
Bone formation rate, cu mm/yr	0.0095	....	0.381 ± 0.152*

*Mean ± standard deviation.

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ABBREVIATIONS USED IN TEXT
AST = aspartate aminotransferase
SD = standard deviation

decreased with an osteoid seam width of less than 6 microns, a fractional resorption surface of less than 3% and fractional double-labeled surface of less than 1%. The osteoid volume was uncalculable (none of the grid reticule points fell on osteoid). However, there was a notable amount of trabecular surface covered with very thin osteoid seams such that the fractional osteoid surface measurement was at the mean for normal. The mineralization lag time was depressed at 0.618 years and the bone formation rate was severely depressed.

A pelvic radiograph done eight months after that shown in Figure 1 and before any therapy was begun showed no further evidence of healing. Therapy with a combination of sodium fluoride, vitamin D and calcium was begun but, despite therapeutic serum concentrations of fluoride, there had been no further improvement in the radiographic appearance of the pelvic fractures after ten months of therapy.

Case 2

The patient, a 75-year-old woman, was referred to the Bone and Mineral Clinic at The Oregon Health Sciences University for evaluation of bone disease. She had been well until 12 years earlier when she began to experience back discomfort. Five years before the current evaluation, the diagnosis of Paget's disease or osteomalacia, or both, had been made on the basis of bilateral femoral diaphyseal pseudofractures and an elevated serum alkaline phosphatase level. A regimen of porcine calcitonin, 100 IU given subcutaneously three times per week, was begun for presumed Paget's disease, and 50,000 units of ergocalciferol with 1,500 mg of calcium carbonate per day was administered for presumed osteomalacia. She subsequently sustained several vertebral crush fractures, a right femoral shaft fracture through the pseudofracture and, finally, six months before evaluation, a left femoral shaft fracture at a site distinct from the pseudofracture. All fractures were associated with minimal trauma.

She had undergone a natural menopause 20 years previously and was started on a regimen of diethylstilbestrol at age 72. Vaginal bleeding prompted a hysterectomy eight months later but she continued the diethylstilbestrol therapy. A benign thyroid nodule had been removed at age 68 and the patient received 3 grains of desiccated thyroid daily thereafter. A mastectomy had been done 15 years earlier for a malignant lesion but there was no evidence of recurrent disease. There was no history of other systemic disease, operations or of other medications known to affect bone metabolism.

On physical examination her weight appeared normal, she had only slight kyphosis and was without bone tenderness. Laboratory studies elicited the following values: serum creatinine, 0.7, calcium, 10.7 (normal, 8.5 to 10.5), and phosphorus, 4 mg per dl; total protein, 7.4 grams per dl, and alkaline phosphatase, 181 mU per ml (normal, 35 to 105). Serum AST and bilirubin concentrations were normal. The serum free thyroxine concentration was 1.1 ng per dl (normal, 0.7 to 1.8). A 24-hour urine calcium excretion was 148 mg while on a routine diet. The serum 25-hydroxycholecalciferol level was 152 ng per ml.

A radiographic evaluation showed generalized osteopenia, multiple wedge and compression fractures of the thoracic and lumbar spine and a pseudofracture of the medial aspect of the proximal left femoral shaft (Figure 2, left and middle). Orthopedic plates were present at the site of repair of the previous right femoral fracture, but a linear lucent zone at the site of the fracture had not yet healed (Figure 2, right). Reviews of previous femoral radiographs showed that a pseudofracture very similar to the one apparent in the left femoral shaft had been present at the site of the right femoral fracture.

Radial-photon absorptiometry done at the junction of the distal and middle thirds of the radius showed a bone mineral content of 0.48 grams, a bone width of 1.08 cm and a bone mineral content/bone width of 0.44 grams per cm^2 (normal, $0.57 \pm .085$ [SD]). At the distal radial site (2 cm proximal to the tip of the ulnar styloid) the bone mineral content was 0.51 grams, bone width was 2.28 cm and bone mineral content/bone width was 0.22 grams per cm^2 (normal, 0.4 ± 0.103 [SD]).

Histologic review of bone material obtained at the time the right femoral fracture was reduced five years earlier showed no evidence of Paget's disease, and a further review of radiographic examinations showed no lesions characteristic of Paget's disease. Histologic sections of bone from the reduction of the left femoral fracture were not available. A percutaneous trephine bone biopsy was done and an 8-mm specimen obtained from the left iliac crest was processed by nondecalcifying methods,[7] sectioned and stained for histomorphometric

Figure 1.—Pelvic radiograph of patient 1 showing pseudofractures (arrows) of pelvic rami.

analysis (Robert Recker, MD). That analysis (Table 1) showed greatly depressed trabecular bone volume (5%). Static measures of bone remodeling showed a fractional osteoid surface of 14% and a fractional resorption surface of 6%. Because the trabecular bone volume was very low and there was very little osteoid present, no grid points fell on osteoid and thus the osteoid volume was not derived. There was very little trabecular bone surface on which formation rates could take place and there were no double labels present on trabecular surfaces (fractional double-label surface, mineralization lag time and bone formation rate were therefore not calculated). Nevertheless, trabecular remodeling was apparently depressed. Several areas of double tetracycline labeling appeared on cortical endosteal surfaces, indicating that the patient had taken and absorbed the tetracycline.

The ergocalciferol therapy was discontinued and the serum calcium level subsequently became normal. Other drug therapy was continued and sodium fluoride was added to the regimen. After eight months the patient had sustained several more thoracic vertebral crush fractures but was tolerating the sodium fluoride well. A repeat radiographic examination of the femurs showed no futher evidence of fracture healing.

Discussion

In 1930 Milkman[4] described a case of a patient with nephritis and a generalized skeletal disorder characterized radiographically by osteopenia and multiple, symmetric, ribbonlike zones of decalcification or "pseudofractures." He later termed the condition "multiple spontaneous idiopathic symmetrical fractures" and suggested it represented a new skeletal disease of unknown cause.[8] The actual clinical implications of the presence of pseudofractures evoked considerable controversy[9,10] until 1946 when Albright and co-workers[11] argued convincingly that pseudofractures in fact represent a manifestation of osteomalacia of any cause. They cited work by Looser who had extensively studied the phenomenon of pseudofractures and concluded that mechanical irritation and local microfracture resulted in callous formation within bone.[12,13] The mineralization defect of osteomalacia prevents this "zone of transformation" (umbauzonen) from mineralizing and a radiolucent area (pseudofracture) results. In fact, the histologic appearance of pseudofracture in osteomalacia is indeed that of unmineralized callus.[12] Whereas radiolucent defects similar to pseudofractures may occur in cases of Paget's disease or osteogenesis imperfecta, the other radiographic manifestations of those disorders are always present as well.[11] Stress fractures, another cause of radiolucent zones similar in appearance to pseudofractures, are a result of mechanical stress and heal rapidly following relief of that stress. Albright and associates concluded, therefore, that "ribbon-like zones of decalcification, which occur in otherwise normal-appearing bone, which last months or years without regressing, and which exhibit a marked tendency to be symmetrical, occur only in osteomalacia or rickets."[11] The perception that pseudofractures are a pathognomonic feature of osteomalacia persists in recent reviews.[5,6]

In contrast, the patients in the two cases reported here manifested radiographic lesions indistinguishable from pseudofractures in their appearance and symmetry. Although the inciting events resulting in the appearance of the fractures are unknown (acute or prolonged mechanical stress, perhaps related to the chiropractic manipulation in case 1), their duration is inconsistent with simple traumatic fracture or stress fracture. Whereas the lesions were not in themselves histologically evaluated, histomorphometric analysis of iliac crest bone biopsy specimens in each case showed osteoporosis with greatly depressed indices of bone remodeling. In both cases the presence of pseudofractures resulted in the initial diagnosis of osteomalacia. In case 2 the therapy for presumed

Figure 2.—Left, Radiograph of proximal left femur of patient in case 2 showing femoral pseudofracture (arrow). **Middle,** Close-up of left femoral pseudofracture (arrow). **Right,** Right femoral radiograph showing zone of lucency at the site of a previous fracture.

TABLE 2.—*Clinical Characteristics of Six Women With Pseudofractures in the Absence of Osteomalacia*

Case	Age	Fracture Location	Serum Calcium	Serum Phosphorus	Alkaline Phosphatase	Bone Histomorphometry	Source
1	73	Pelvis	N	N	Elevated	Low-turnover osteoporosis	This study
2	75	Femur	N	N	Elevated	Low-turnover osteoporosis	This study
3	40	Multiple	N	N	N	. . .	Richardson et al, 1978[14]
4	34	Multiple	N	N	N	. . .	Richardson et al, 1978[14]
5	64	Femur	N	N	N	. . .	Perry et al, 1982[15]
6	33	Femur	N	N	N	. . .	Perry et al, 1982[15]

*N = normal

osteomalacia of ergocalciferol and calcium was associated with supranormal concentrations of 25-hydroxycholecalciferol and hypercalcemia, which resolved with discontinuance of the ergocalciferol. The pathophysiology of the osteopenia in these two patients is unknown but several potential risk factors were present in each patient—case 1: age, postmenopausal state and aluminum-containing antacid use; case 2: age, postmenopausal state, desiccated thyroid therapy, ergocalciferol therapy. In case 2 calcitonin therapy probably did not contribute to a progression of osteopenia.

Several other patients have had pseudofractures occurring in the absence of osteomalacia. Richardson and colleagues[14] reported the cases of two premenopausal women who presented with skeletal pain of five to ten years' duration, multiple pseudofractures (nonsymmetric) and no biochemical or histologic evidence of osteomalacia. Treatment with a regimen of calcium and vitamin D resulted in no improvement. Similarly, Perry and associates[15] described the cases of two women (one premenopausal and one postmenopausal) who presented with bilateral, painful femoral pseudofractures of nine months' and eight years' duration. Once again there was no biochemical or histologic evidence of osteomalacia. In one patient, treatment with calcium and vitamin D for presumed osteomalacia resulted in the prompt development of hypercalcemia. A traumatic completion of a femoral neck pseudofracture subsequently occurred, and nonhealing eventually resulted in the need for a total hip replacement.

In Table 2 the clinical characteristics of the two cases described here are shown with those of the four previously reported cases. All were women (three were premenopausal and three postmenopausal) and three had other roentgenographic evidence of osteopenia (vertebral compression fractures). The location of the pseudofractures was most commonly femoral (five of six) but included a wide variety of sites. In four women, all routine biochemical variables were normal, whereas in two there were slight elevations in the serum alkaline phosphatase concentration. Bone histology was characterized by the absence of osteomalacia in all, and pronounced trabecular osteopenia with severely reduced bone remodeling was found in the two present cases. In two patients the treatment of presumed osteomalacia with vitamin D and calcium resulted in the development of hypercalcemia, which was quickly corrected with the withdrawal of therapy. Finally, the potential seriousness of the syndrome is underscored by the occurrence of completed femoral fractures in two patients.

These cases show that multiple pseudofractures characterized by symmetry and delayed resolution are not always the result of an osteomalacic process, and that the metabolic bone disease underlying the development of pseudofractures may include osteoporosis. Potentially more appropriate therapy for osteoporosis was considerably delayed in these patients by the erroneous diagnosis and therapy for osteomalacia. Furthermore, the occurrence of hypercalcemia in two patients with this syndrome (during treatment with vitamin D and calcium) illustrates the risks of treating for presumed osteomalacia without histologic verification. These cases indicate the diagnostic value of the percutaneous bone biopsy and bone histomorphometry, particularly in the absence of the biochemical concomitants of osteomalacia (hypocalcemia, hypophosphatemia and elevated alkaline phosphatase concentration).

The pathophysiology of pseudofractures in the absence of osteomalacia is unknown but may involve defects in new bone formation and a resultant inadequacy of repair at sites of stress or microfracture (the Looser hypothesis). In the two cases reported here, the pronounced depression in bone remodeling and specifically in the rate of new bone formation may have prevented an appropriate healing response, resulting in the development of pseudofractures.

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Chronic Myelocytic Leukemia as a Secondary Malignant Condition in a Patient Receiving Prolonged Chemotherapy for Ovarian Carcinoma

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THE DEVELOPMENT OF secondary malignant conditions in patients who have received chemotherapy for their primary neoplasm is becoming an increasingly recognized and major problem in clinical oncology.[1,2] In cases of ovarian carcinoma, several investigators have found a significantly increased risk for the development of secondary acute nonlymphocytic leukemia in women who have received alkylating agents as therapy for their disease.[3-6] In this report I document the occurrence of an extremely rarely reported secondary malignant disorder, chronic myelocytic leukemia, in a patient who had been given chemotherapy for several years for advanced ovarian carcinoma.

Report of a Case

The patient, a 44-year-old woman, was diagnosed as having stage III poorly differentiated adenocarcinoma of the ovary in March 1980. Following a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and tumor debulking, the patient was treated with intravenous administration of cyclophosphamide and doxorubicin hydrochloride. A second-look laparotomy showed residual tumor and the patient was subsequently given eight courses of cisplatin followed by a daily oral regimen of cyclophosphamide for 11 months. Unfortunately, the tumor recurred and an experimental intraperitoneal chemotherapy program was begun that included the administration of cisplatin, cytarabine and doxorubicin on a monthly basis.[7] This treatment was continued for about a year. Leukocyte counts from March 1980 through January 1984 were within the normal range. In February 1984 the leukocyte count had increased to 24,000 per μl and by May 1984 the value was 74,000 per μl. The platelet count had also increased from the normal range to 750,000 per μl in May. Review of the patient's peripheral blood smear showed immature leukocytes (no blast forms) and 2% basophils. On physical examination in May the presence of a palpable spleen was noted for the first time. Due to the patient's poor clinical condition a bone marrow aspirate was not done but a karyotype analysis of the peripheral blood showed the presence of the Philadelphia chromosome—46,XX,t(9,22)—in all the metaphases examined. No specific therapy was instituted and the patient died a month later. The approximate cumulative doses of chemotherapeutic agents the patient received during her illness included 30 grams of cyclophosphamide, 600 mg of doxorubicin, 14 grams of cytarabine and 3.6 grams of cisplatin.

Comment

To the best of my knowledge, this is the first report of chronic myelocytic leukemia developing in a patient receiving chemotherapy for ovarian carcinoma. Several cases have been reported in patients receiving long-term immunosuppressive therapy for renal transplants,[8] and two additional cases have been described of patients with malignant disease (acute lymphoblastic leukemia and Hodgkin's disease)[9,10] receiving chemotherapy in whom chronic myelocytic leukemia developed as a secondary disease process.

While it is certainly possible that the development of chronic myelocytic leukemia in this patient is completely unrelated to her prior chemotherapy, it is reasonable to hypothesize that the almost continuous therapy she received from the onset of her disease in March 1980 until her leukocyte count began rising in February 1984 was somehow implicated in the pathogenesis of this second malignant process. In particular, this patient was treated long term with alkylating agents, which have been most often linked with the occurrence of secondary acute nonlymphocytic leukemia.[1-6] Alkylating agents include cyclophosphamide, melphalan, chlorambucil, thiotepa and mechlorethamine (nitrogen mustard).

It is possible that additional cases of chronic myelocytic leukemia developing as a consequence of therapy might not be recognized unless specifically looked for in the case of a rising leukocyte count, and the presence of immature granulocytes in the peripheral blood can be easily passed off as a leukemoid reaction to the primary malignant lesion.

(Markman M: Chronic myelocytic leukemia as a secondary malignant condition in a patient receiving prolonged chemotherapy for ovarian carcinoma. West J Med 1985 Aug; 143:243)

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Gastrointestinal Histoplasmosis in Suspected Acquired Immunodeficiency Syndrome

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"ACQUIRED IMMUNODEFICIENCY SYNDROME" is a term used in describing a group of patients who have a profound state of immunologic compromise so that opportunistic infections and a variety of malignant neoplasms develop. The syndrome has assumed epidemic proportions since its recognition in mid-1981.[1-3] Initially described in homosexual men and intravenous drug abusers, additional groups now include Haitian refugees,[4,5] hemophiliacs receiving factor VIII concentrates,[6-8] transfusion recipients,[9] female sexual partners of men with the syndrome,[10] prison inmates[11] and infants in high-risk households.[12,13]

Disseminated histoplasmosis is a rare opportunistic infection occurring in a setting of compromised cellular immunity.[14] Though cases have been recognized in patients with acquired immunodeficiency syndrome,[15,16] very few have been reported to the Centers for Disease Control (CDC). In this report, we describe a case of *Histoplasma*-induced granulomatous colitis seen in a male homosexual as a cecal mass that appeared to be carcinoma. The patient's disseminated fungal infection was associated with autoimmune thrombocytopenia and hypoproliferative anemia. Treatment consisted of surgical resection followed by administration of amphotericin B. To date, no similar case has been described in the literature, nor have any cases of granulomatous colitis caused by *Histoplasma capsulatum* been reported to the AIDS Task Force of the Centers for Disease Control. The fact that the patient presented in a nonendemic area emphasizes the necessity to obtain a thorough history of antecedent travel and exposure.

Report of a Case

A 38-year-old homosexual man was admitted to Stanford University Medical Center for surgical resection of a right lower quadrant mass.

The patient, a resident of northern California for several years, was born and raised in the state of Kentucky. He had returned yearly to the midwest since moving to the West Coast in the early 1970s. The patient had led a homosexual life-style since puberty, having had sexual relations with approximately 200 different partners. His medical history included many episodes of gonorrhea, with two episodes of gonorrhea-induced proctitis. The patient had had recurrent vesicular lesions involving the labial and perianal areas.

Three weeks before admission, the patient consulted his local physician after having for six days dull, continuous right lower quadrant pain unrelated to meals. He had experienced no nausea, vomiting, diaphoresis or malaise, but had noted some looseness of his stools as well as intermittent fevers to 38.5°C (101.3°F). On abdominal examination, the patient had moderate right lower quadrant tenderness without rebound, masses or palpable organs. The right costovertebral angle was minimally tender. A complete blood count showed a hemoglobin of 14.3 grams per dl, a hematocrit of 42.4%, and a leukocyte count of 7,100 per μl with 56% segmented neutrophils, 3% band neutrophils, 20% lymphocytes, 8% monocytes, 10% eosinophils and 3% basophils. Platelets were 85,000 per μl: Results of a serum chemistry profile (SMA-20) were unremarkable. A urine specimen had 4 to 6 erythrocytes per high-power field, with few leukocytes. Culture of a urine specimen was negative for routine pathogens as well as for *Neisseria gonorrheae*. Examination of a stool specimen showed few neutrophils, a moderate number of yeast forms and no ova or parasites.

No specific therapy was begun. The patient's symptoms persisted and blood and urine values remained unchanged. To exclude the possibility of renal colic, an intravenous pyelogram was done; results were within normal limits. A Westergren erythrocyte sedimentation rate was 61 mm per hour (normal $\leq$ 15 mm per hour). A fluorescent antinuclear antibody test was negative and serum complement values were within normal limits.

The patient was referred to the Palo Alto Medical Research Foundation for evaluation. On initial physical examination the patient had moderate right lower quadrant abdominal tenderness with a firm palpable mass. A barium enema showed an intraluminal cecal lesion highly suggestive

Figure 1.—Barium enema showing cecal mass.

(Haggerty CM, Britton MC, Dorman JM, et al: Gastrointestinal histoplasmosis in suspected acquired immunodeficiency syndrome. West J Med 1985 Aug; 143:244-246)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control

of carcinoma (Figure 1). As part of the patient's evaluation, lymphocyte subtyping was done and was notable for an Leu3:Leu2 ratio of 0.12. The total T-cell number (Leu4) was 829 (normal 1,200 to 1,800), with a notably reduced T-helper subpopulation (Leu3 = 90; normal 600 to 1,200) and moderately increased T-suppressor/cytotoxic subpopulation (Leu2 = 739; normal 350 to 600). Results of skin testing revealed anergy to purified protein derivative, mumps, coccidioidin and dermatophyton. A blood specimen was negative for hepatitis B surface antigen. Epstein-Barr antibody titers were consistent with prior infection (viral capsid antigens 1:320; Epstein-Barr nuclear antigen 1:80; early antigen, diffuse and restricted, $< 1:5$). Cytomegalovirus and toxoplasma antibody titers were 1:128 and 1:16, respectively. Quantitative platelet-associated antibody was significantly elevated at 13.5 femtogram IgG per platelet (normal ≤ 5.3).

The patient was admitted to Stanford University Medical Center for resection of the cecal mass. Laboratory evaluation on admission showed the following: a hemoglobin of 11.1 grams per dl, a hematocrit of 33.4% and a leukocyte count of 4,700 per μl (47% segmented neutrophils, 11% band neutrophils, 29% lymphocytes, 6% monocytes and 7% eosinophils). The platelet count was 90,000 per μl. A urine specimen contained no erythrocytes and a chest roentgenogram was normal. At operation the patient had a large inflammatory mass involving the right colon and the greater omentum. There was extensive mesenteric lymphadenopathy and numerous serosal implants.

Pathologic examination of the resected right colon showed a circumferential lesion near the ileocecal valve measuring 4 by 7 cm and having a "heaped-up," ulcerated appearance (Figure 2). On sectioning, the mass was found to be composed of firm, white, coarse tissue extending through the colonic wall and into the pericolonic fat. The adjacent mesocolon was thickened and contained a chain of enlarged lymph nodes. Microscopic examination showed intense noncaseating granulomatous inflammation. Stains for acid-fast organisms were negative, but stains for fungi showed striking infestation with budding yeast forms, occurring intracellularly and extracellularly. Cultures of all specimens grew *H capsulatum*. A left iliac bone marrow biopsy specimen obtained at laparotomy showed normal cellularity without granulomas and was negative for pathogens when cultured.

The patient's postoperative course was uncomplicated. His hematocrit continued to decrease, and he ultimately required transfusion. Stool specimens were intermittently positive for occult blood. A reticulocyte count was 0.3%. Mean corpuscular volume was 84 cu microns. The serum iron value was 64 μg per dl (normal value is 40 to 140 μg per dl) and total iron-binding capacity was 144 μg per dl (normal 250 to 400 μg per dl), yielding a saturation of 44%. Direct and indirect Coombs' testing was negative. The platelet count stabilized at 90,000 per μl. On the sixth postoperative day, therapy with amphotericin B was begun and the patient ultimately received a total dose of 2.5 grams over the ensuing three months.

Shortly after discharge, a cough developed and the patient had a pulmonary infiltrate suggestive of early *Pneumocystis* pneumonia. Fiberoptic bronchoscopy with transbronchial biopsy and bronchoalveolar lavage were negative for parasitic, fungal, bacterial or neoplastic disease. The patient's pneumonitis resolved without specific therapy. At the time this manuscript was prepared (four months after completion of amphotericin therapy), the patient had no signs or symptoms of disseminated histoplasmosis or other opportunistic infection. Repeat lymphocyte subtyping has yielded abnormal results nearly identical to those previously obtained.

Discussion

This case helps to establish *Histoplasma capsulatum* as a pathogen that must be considered in patients with the acquired immunodeficiency syndrome (AIDS). As the current case definition of the CDC does not include disseminated histoplasmosis, our patient does not strictly satisfy the criteria for AIDS. Nevertheless, because dissemination is rare in otherwise normal persons, this case argues for the addition of disseminated histoplasmosis to the list of fungal infections in the CDC's criteria. The fact that this infection manifested itself in a nonendemic area demonstrates the necessity of obtaining an accurate travel history and the importance of considering endogenous reinfection in immunologically suppressed patients.[17] This is especially pertinent because

Figure 2.—Gross pathologic appearance of resected right colon with cecal mass.

most cases of AIDS are reported from areas where histoplasmosis is not a prevalent infectious disease problem.[18]

Gastrointestinal tract involvement occurs in up to 75% of cases of disseminated histoplasmosis.[14,19] Nevertheless, clinically obvious gastrointestinal involvement is infrequent and oral lesions are far more common than colonic manifestations. In cases where the colon is involved, the lesion usually begins as an elevated plaque, with progression to a localized granulomatous ulcer. Uncommonly, such foci will assume a different pattern of growth, resulting in a mass that can simulate carcinoma as a constricting ("apple core") lesion[19] or, as in our patient, as a fungating intraluminal tumor.

The presence of autoimmune thrombocytopenia in this patient is an interesting finding. Morris and associates have described patients with AIDS who were also noted to have thrombocytopenia and elevated platelet IgG values.[20] *Histoplasma*-induced autoimmune thrombocytopenia has likewise been reported.[21] Whether AIDS or *Histoplasma*-induced thrombocytopenia is important in this case cannot be determined.

Although cases of hemolytic and hypoproliferative anemia have been reported in patients with Kaposi's sarcoma,[22,23] anemia is not recognized as a common manifestation of AIDS per se. Our patient had an inadequate marrow response to continued postoperative gastrointestinal blood loss. His serum iron and iron-binding capacity are consistent with what has been recognized as "anemia of chronic inflammation."

Untreated, the mortality of disseminated histoplasmosis in patients who do not have this syndrome has been as high as 83%.[24] The efficacy of therapy with amphotericin B is well established, although total dosages must exceed 2 grams.[25] Ketoconazole has been effective in selected cases of disseminated histoplasmosis and its use is associated with far less toxicity than for amphotericin B.[26] This new imidazole derivative would have been particularly advantageous for our patient, given his increased likelihood for new fungal infections that would require additional amphotericin B. Unfortunately, ketoconazole's efficacy for treatment of disseminated histoplasmosis in immunosuppressed patients has been disappointing.[27,28]

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Factitious Hematuria and Self-Induced *Candida albicans* Fungemia

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PATIENTS WITH FACTITIOUS disorders are characterized by their conscious production of spurious historical, physical or laboratory data for no apparent reason other than to assume the patient role.[1] These patients represent a diverse psychiatric group and may simulate a wide variety of medical problems. In this report we describe a case of a patient with factitious hematuria, fever and *Candida albicans* fungemia and review the diagnosis and management of factitious disorders.

(Gordon GH, Chrys R: Factitious hematuria and self-induced *Candida albicans* fungemia. West J Med 1985 Aug; 143:246-249)

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Report of a Case

The patient, a 23-year-old man, presented to an emergency room with a two-day history of right lower quadrant pain and gross hematuria accompanied by nausea, vomiting and mild dysuria. He stated that his right kidney had been "ruptured" during a parachute jump while he was serving military duty in 1978, producing transient hematuria. He also gave a history of operations in 1979 and 1982 to "straighten a kinked ureter" on the right and an appendectomy in 1980. There was no history of nephrolithiasis, dysuria, fever or recent trauma.

On physical examination he was in mild distress, with an oral temperature of 36.6°C (97.3°F), pulse 74 beats per minute, blood pressure 100/70 mm of mercury and respiratory rate 16. Positive physical findings were limited to the abdomen. Two midline surgical scars extended from the umbilicus to the pubis and an appendectomy scar was present. Bowel sounds were normal. There was tenderness to light palpation in the right lower quadrant without guarding or rebound tenderness and he had a 3-cm right inguinal hernia that was easily reducible. Results of rectal and genital examinations were normal and there was no tenderness at the costovertebral angle. Laboratory data included an analysis of urine showing erythrocytes too numerous to count, 0 to 2 leukocytes per high power field, 1+ protein and no bacteria. Serum glucose level, electrolytes, complete blood count, prothrombin time, partial thromboplastin time, platelet count and blood urea nitrogen and serum creatinine levels were all normal. X-ray films of the chest and abdomen also were normal.

The patient was admitted to the Urology Service where an intravenous pyelogram showed an ectopic and malrotated right pelvic kidney with mild pyelocaliectasis. The right ureter was short but of normal caliber, and the left kidney was normal. Cystoscopy and retrograde pyelography failed to show a source of bleeding. On renal angiography there were double renal arteries on both sides but no other abnormalities. A urine specimen obtained by catheterization contained no blood. The patient's abdominal pain continued and he requested frequent parenteral administration of narcotics. Several institutions where he claimed to have received treatment had no record of his care. Factitious hematuria was suspected, and the nursing staff was instructed to observe the patient urinate.

On the seventh through the tenth hospital days, oral temperature elevations were recorded ranging from 39°C (101.7°F) to 40.7°C (104.7°F). Temperature elevations were unaccompanied by tachycardia or leukocytosis. Cultures of blood and urine specimens were carried out and empiric antibiotic therapy for a presumptive urinary tract infection was begun. By the 18th hospital day the patient's hematuria and fever had resolved, but culture of four of eight blood specimens obtained on three separate days during his febrile episodes grew *Candida albicans*. The patient was transferred to the Medical Service where a careful physical examination showed no evidence of fungal endocarditis or disseminated fungal infection. One day following transfer, the patient complained of a stiff neck and was found to have an oral temperature of 38.6°C (101.0°F). A lumbar puncture was done that yielded clear fluid with a glucose level of 72 mg per dl, a protein value of 41 mg per dl and no cells. Cultures of two more blood specimens taken on the day of transfer agai grew *C albicans*. Cultures of several urine and throat speci mens showed no growth of *Candida*, and an echocardiogram, gallium scan and computed tomographic study of the abdomen failed to show a focus of infection.

On the 22nd hospital day, acting on information received from a roommate, the patient's personal belongings were searched and several tuberculin syringes and a vial of milky-white substance were recovered. Laboratory analysis showed that the substance was magnesium-containing antacid that grew *C albicans* on culture. When the patient was confronted with these findings, he confessed to injecting the substance intravenously through the antecubital fossa. He said he did not know that the antacid was contaminated and that he injected himself to relieve pain and to draw attention to his inguinal hernia, which he wanted repaired. After the vial and syringes were removed from the bedside, the patient's fevers disappeared and eight subsequent blood cultures were negative for *C albicans*.

Psychiatric consultation was obtained, and the patient was transferred voluntarily to the Psychiatry Service. He stated that his parents had divorced when he was 6 months old and that he had been raised by his father, in whom a chronic illness developed following radiation exposure during military duty. The patient believed that his pelvic kidney and inguinal hernia were genetic defects related to his father's radiation exposure. He admitted that he had abused drugs intravenously in the past and recently had been released from prison in Texas after serving a one-year term for passing bad checks. He reported having difficulty reintegrating into society and requested that his hospital discharge be delayed until he could make plans for living outside the hospital. It was discovered that the patient had been admitted to hospital with hematuria in the San Diego Veterans Administration Medical Center one month before admission but had used a false social security number and military service dates. Results of psychological testing indicated poor insight and impulse control and a tendency to somatize anxiety. He became increasingly hostile and noncompliant on the Psychiatry Service and was discharged on the 58th hospital day with a psychiatric diagnosis of borderline personality disorder with histrionic and schizoid features, and adjustment disorder with anxious and depressed mood.

Comment

Factitious Disorders

The incidence of factitious disorders, particularly among outpatients, is unknown; however, 41 inpatient cases were reported from a teaching hospital during a ten-year period.[2] Patients with factitious disorders may present with symptoms and signs referable to any organ system. The complaints may be either dramatic and urgent or complex and subtle. As in the case reported here, the presence of a preexisting pathologic condition or a self-induced pathophysiologic state can make a spurious history seem more credible. Patients may also present with several simultaneous factitious disorders.[2-5]

Gross hematuria with or without renal colic is a common factitious disorder and may be produced by adding blood to urine after voiding or by traumatizing the urethra.[3,4,6-10] Some patients can actually simulate the roentgenographic appearance or passage of renal calculi.[9,10] Although ectopic or

malrotated kidneys may be associated with abdominal or flank pain, pyuria, proteinuria and recurrent urinary tract infections.[11] it seems likely that our patient's hematuria was factitious because results of analysis of urine were otherwise unremarkable and because urine obtained by catheterization never contained blood.

Factitious fever is also a well-documented syndrome, with a prevalence of 2% to 9% in patients with fever of unknown origin in several large series.[3-5,12,13] Factitious fever may be produced by various methods of thermometer manipulation or by self-injection of contaminated or pyrogenic substances. Thermometer manipulation results in the apparent loss of normal diurnal temperature variation and is unaccompanied by skin warmth, tachycardia, diaphoresis and leukocytosis when thermometer readings are elevated. Elevated thermometer readings produced by thermometer manipulation may differ greatly from temperature readings obtained with a nurse or physician in constant attendance, or from different body orifices, leading to the appearance of widely and rapidly fluctuating thermometer readings.[3,5] Our patient's temperature readings were taken in the presence of hospital staff but were unaccompanied by tachycardia or leukocytosis. His fevers may have been a physiologic response to the injection of foreign, contaminated material; on the other hand, fever in the setting of another factitious illness is often itself factitious, and patients with self-induced infections have been known to manipulate their thermometers.[4,5]

In two recent reports, self-induced infections accounted for 41% of cases of factitious fever[5] and 30% of all cases of factitious disorders.[2] The most frequent clinical presentations of self-induced infections are chronic recurrent subcutaneous abscesses and bacteremias. A pattern of several infections over many years is usual before the factitious cause is recognized. Self-injection from syringes filled with contaminated substances is a common method of inoculation, and Gram-negative enteric organisms and Gram-positive cocci are the usual pathogens. Most self-induced infections are simultaneously or consecutively polymicrobial unless pure bacterial cultures are injected.[5,13] Other materials that have been injected include air, dirt, saliva, human and animal feces, foot washings, tetanus toxoid, milk, deodorant, alcohol and lighter fluid.[4,5,13] Our computerized search of the medical literature failed to find published reports of the self-administration or effects of oral antacid preparations given parenterally. Furthermore, we found only two cases of *C albicans* fungemia associated with self-induced infection.[5,13] Both were associated with cases of polymicrobial bacteremia, and one was felt to be due to a contaminated intravenous catheter.[5] Although *Candida* endocarditis has been described in intravenous drug abusers, *C albicans* fungemia associated with infected urinary or intravenous catheters may resolve spontaneously in immunocompetent hosts following catheter removal.[14] After we removed the contaminated vial and syringes from the bedside, blood cultures for *C albicans* were persistently negative and the patient had a benign clinical course, indicating that neither endocarditis nor disseminated tissue invasion was present.

Psychopathology

Psychiatrically, patients with factitious disorders are a heterogeneous group with diagnoses including neurosis, personality disorders, organic mental states and psychosis.[15] Some have borderline personality disorder, which is characterized by intense anger and depression, impulsive self-destructive behavior, unstable relationships with others (including physicians) and brief episodes of psychosis.[5,16] Patients with factitious disorders may have a history of early rejection or abandonment by their parents or early exposure to chronic illness, physicians or institutional care. They also may have education or experience in medically related areas and real or imagined physical abnormalities. For some of these patients, admission to hospital and care by physicians and nurses may represent an unconscious reenactment of disturbances in early relationships with parents over issues of trust, dependency, mastery, aggression and guilt.[17,18]

Some patients produce only one or occasional factitious disorders in response to stress and have no other evidence of psychiatric impairment. Others with a variant of factitious disorder termed Munchausen's syndrome have a history of drug abuse and sociopathic, criminal or psychotic behavior that is obscured by their gross impostures and pathological lying.[15-18] Although pain control is often an issue, they readily accept painful invasive procedures. These patients travel widely, simulate abdominal, hemorrhagic or other emergencies and may leave a hospital abruptly following a hostile confrontation with their physicians. Our patient's history of drug abuse and imposture and his hostile, noncompliant response to psychiatric hospital admission suggest that he belongs in this Munchausen's syndrome subgroup. Patients with another variant of factitious disorder have been described as immature, passive and hypochondriacal.[2,4] These patients are more likely to be young women and to have worked or trained in a medically related field. They are also more likely to respond favorably to confrontation and ongoing medical or psychiatric care. Patients in any of these groups may present with severe or life-threatening factitious disorders.

Diagnosis

Patients with factitious disorders usually present unduly long, complex or improbable histories filled with medical or pseudomedical terminology. Early recognition of these disorders, therefore, requires that historical or other inconsistencies be clarified as they arise. Other hospitals and physicians, insurance companies, employers or relatives may also provide useful diagnostic information. Once a factitious disorder is suspected, the patient should be observed carefully for behavior confirming this diagnosis. Occasionally, as in the case reported here, materials used to produce the factitious disorder may be discovered. When enough evidence to suggest the diagnosis has been gathered, the patient should be confronted in a supportive and nonthreatening manner, without implying abandonment by the primary physician.[2,5,13,16] Plans for continued medical and psychiatric treatment should be presented to the patient at the time of confrontation. Although confrontation rarely results in confession, even when the evidence is convincing, it may relieve an impasse between the patient and the medical staff or result in disappearance of the factitious disease. A few patients make their deception so obvious that they seem to invite confrontation and leave the hospital angrily after a short stay. In others, confrontation may lead to further self-destructive be-

havior or flight from treatment.[8] A psychiatric consultant may help to identify patients at high risk for reacting poorly to confrontation and may also assist with the confrontation process.

Treatment

The patient in the case reported here may have accepted psychiatric treatment as a condition of continued hospital stay. Most patients with factitious disorders are resistant to psychiatric intervention, however, and no psychiatric treatment approaches have proved consistently effective.[15,16] Many of these patients are also unable to maintain a therapeutic relationship with a primary care physician, and their long-term medical care is often fragmented and episodic. Patients who are willing to be followed in a primary care setting should be given careful medical evaluations, and those who are overly concerned about a real or imagined physical abnormality should be reassured. A schedule of regular outpatient visits should then be established.[19] This schedule relieves the patient's fears of abandonment by the physician and removes the contingency of further visits on the presence of disease. During the actual visits, a supportive, noninterpretive approach should be taken and healthy psychosocial behaviors such as appropriate recognition and expression of feelings should be reinforced by the physician's interest and approval. Formal contracts may be used to limit the use of medications, procedures and visits to other physicians and the production of factitious disease. For patients with borderline personality disorder, unrealistic expectations for care and dramatic responses to disappointment should be anticipated.[5,16] Because borderline patients frequently characterize others as "all good" or "all bad," physicians and staff must agree on a consistent treatment approach. It must be emphasized that patients with factitious disorders are poorly understood and that many are incorrigible or present major treatment problems. Physicians who expect patients to become cured, insightful or grateful will need to lower these expectations to avoid anger and disappointment.

A key aspect of treatment is avoiding negative attitudes toward the patient. Although these patients intentionally mislead or manipulate physicians, many regard physicians as allies and do not derive pleasure from deceiving them. Physicians should thus regard the production of factitious disease as an emotional disorder rather than malicious trickery.[2,10] Anger at the patient may result in an exaggerated attitude of mistrust, neglect of coexistent medical problems or outright abandonment. Similarly, guilt related to missing the diagnosis, accusing the patient of lying or feeling helpless may result in an intense or exclusive focus on medical or surgical problems and neglect of pertinent psychosocial issues.[16] Discussing the case with a psychiatrist may help the primary physician exclude other psychiatric disorders and plan an effective management strategy. Although the prognosis for the disappearance of a factitious disorder is guarded for patients with psychosis or borderline personality disorder, patients with good premorbid psychosocial function may recover and have no further factitious episodes.[2]

The diagnosis and management of factitious disorders pose some unique legal and ethical questions.[20] Failing to initiate appropriate emergency care until a true pathophysiologic state is ruled out, circulating photographs of a patient to other physicians or suddenly abandoning a patient may be grounds for a lawsuit. Searching a patient's belongings for evidence of factitious disease without his or her knowledge or consent has been justified on the basis of suicidal risk[2]; however, few of these patients have been successfully committed to psychiatric institutions as a danger to themselves.[15] Finally, the physician's duty to protect a patient's integrity and confidentiality is challenged by the deceit and may conflict with the physician's duty to inform affected family members, other physicians and third-party payers of the factitious nature of the disorder.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Anticholinergic Agents in Cicutoxin Poisoning

TO THE EDITOR: The recent article by Landers and co-workers[1] is an excellent toxicologic review of what is reputed to be the most poisonous plant in North America,[2] the water hemlock. As noted by the authors, previous publications have indicated that cicutoxin-induced seizure activity appears to result from an overstimulation of central cholinergic pathways.[3,4] Starreveld and Hope[4] suggested that perhaps an anticholinergic agent, such as atropine, might be of value in mitigating the convulsive effects of this plant. We have published the results of a study[5] which examined the possible use of anticholinergic agents in the treatment of *Cicuta douglasii* poisoning.

Our study utilized 35-day-old, C-1 mice which were placed, one each, in plastic boxes to avoid any effects of grouping. A dilute alcoholic extract was prepared from the root of verified *Cicuta douglasii.* Dose-effect data on seizure activity were collected using five doses (intraperitoneally) of ten mice per dose. Similar data were collected on mice that had been pretreated with benztropine and biperiden. We found no significant difference in the convulsive dose-50% (CD_{50}) between the control animals and those treated with the anticholinergic agents. In addition to this information, we collected data comparing the CD_{50} of control animals versus animals pretreated with physostigmine. This phase of the study was to examine the hypothesis that cholinergic stimulation would have an additive seizure-inducing effect with concomitantly administered cicutoxin by lowering the seizure threshold. As with the first phase of the study, no significant difference was noted between pretreated mice and controls. The final phase of the study compared control animals with those pretreated with diazepam. In contrast to the initial phases of the study, we found diazepam to significantly elevate the CD_{50} in mice ($P < .05$).

Our results suggest that the convulsive effects of water hemlock are neither reduced by the anticholinergic agents benztropine or biperiden nor increased by the use of the cholinergic agonist physostigmine. Use of diazepam, on the other hand, significantly reduces seizure activity, when compared with findings in controls. As suggested by Landers, and confirmed by our study, cicutoxin-induced seizures should be controlled with intravenous administration of diazepam. We hope that precious time and effort will not be wasted in the clinical setting attempting to utilize central anticholinergic agents in treating water hemlock poisoning.

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A Medicaid Success Story

TO THE EDITOR: Dr Boni's letter "Abolish Medi-Cal"[1] struck a responsive cord in me. We all have our private horror stories to tell about this "system for denying payment for . . . medical care." I would like to share with Dr Boni and other readers a success story involving that same system. This can perhaps give an answer to the question of how physicians in a "less affluent area" can provide care to poor patients through the current Medicaid system (Medi-Cal in California).

It is clear that the current system is a "two tier system"—in fact, if not in theory. The solution we have arrived at accepts this fact and relies upon a combination of Medi-Cal reimbursement and volunteered physician services to provide care to 2,000 or more patients on state aid.

Realizing that "If I continue to treat poor patients it will be at my own expense," many physicians had, in the past, simply refused to treat such patients or severely limited their practices. Medicaid patients had limited access to care and physicians who treated such patients had to pass on their losses to their private sector patients.

In 1983 a group of doctors in my locality organized a nonprofit clinic devoted exclusively to the care of Medi-Cal patients. No other form of reimbursement is accepted. Ordinary outpatient services are provided by nurse practitioners and physician's assistants under close supervision by volunteer physicians in a group practice next door. Patients requiring physician services are seen by a panel of volunteer physicians who staff "clinics" on their own time, free of charge. In serious emergencies, patients are sent to the hospital's emergency room next door. Another group of physi-

cians provide care through their offices for obstetrical or inpatient hospital care on a rotating basis, charging Medi-Cal for their services. The clinic staff does the necessary paperwork and phone calls to obtain treatment authorization from Medi-Cal when hospital admission or surgery is required.

This approach has proved quite successful. Patients are assured the availability of care, and physicians are able to fulfill their desire to do their share of charity care without burdening their offices with Medi-Cal paperwork. The clinic itself has been able to generate enough charges, even at low Medi-Cal reimbursement rates, to pay the overhead and personnel costs.

There is no doubt that the current Medi-Cal program is inefficient, expensive and filled with impediments to reimbursement for provision of medical care. These problems can be solved in part by using physicians' traditional willingness to provide some free care as part of their professional obligation.

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Dysthyroid Ophthalmopathy

To the Editor: We read with interest the article "The Ophthalmopathy of Graves' Disease" in the April 1985 issue.[1] Our experience with several hundred patients with dysthyroid ophthalmopathy has allowed us to formulate a protocol for their management.

During the acute phase, we recommend several supportive measures, including elevation of the head of the bed and artificial tear drops to the eyes. In addition to corneal exposure from proptosis and eyelid retraction, many of these patients have decreased tear production. We feel that control of any thyroid gland abnormalities is important to the general health of the patient, but have not seen any correlation between this control and the progression of the orbitopathy. In general, the orbitopathy tends to run its course. Medicines, surgery and even radiation may make the patient more comfortable, preserve the vision and more rapidly restore function. Nonetheless, the disease process itself must run its course until quiescence is achieved. Prednisone is occasionally of use in patients with severe inflammatory reactions, but should not be used on a regular basis and should not be used for longer than several weeks.

During the acute phase the patient should be examined regularly by an ophthalmologist for evidence of dysthyroid optic neuropathy. This is most likely caused by the enlarging extraocular muscles compressing the optic nerve at the apex. It is interesting to note that in patients with maximal posterior muscle enlargement there is minimal proptosis but often optic neuropathy develops. When optic neuropathy is detected, we institute a trial of corticosteroid therapy for several weeks. Oral administration of prednisone may minimize orbital apex edema and allow the patient to pass through this phase of the orbitopathy without surgical intervention or irradiation. If optic neuropathy persists in a patient on a regimen of 100 mg of prednisone a day for several weeks, surgical orbital decompression is carried out. Careful attention is given to decompression of the orbital apex. It is only after failure of corticosteroids and surgical decompression to relieve the optic neuropathy that we advise radiation therapy. In management of more than 150 cases we have used radiation therapy in three patients. In our experience, irradiation causes extreme fibrosis of the orbital contents and increased difficulty with the patient's future rehabilitation. We strongly feel that radiation therapy for nonmalignant maladies is to be avoided when possible.

Once the acute phase has passed and the patient is stable for six to nine months, surgical rehabilitation may be considered in a stepwise fashion. We feel that there are four sequential stages to this rehabilitation. Stage one is orbital decompression to move the eyes back to a more posterior and protected position in the orbit. Stage two is an extraocular muscle surgical procedure to correct diplopia. Stage three is eyelid malposition correction (such as recession of eyelid retraction). Stage four is removal of excess eyelid skin and fat that has formed as a result of the disease process. Each stage must be considered in order. Any unnecessary stage may be skipped. Surgical rehabilitation done in this order provides better results and keeps the number of procedures to a minimum. For example, strabismus operations carried out on patients with proptosis recess the muscles and allow the globes to become more proptotic. Subsequent orbital decompression moves the eyes and muscle cones posteriorly and often results in a change in muscle cone position with associated induced strabismus. The patient then requires an additional strabismus operation. Movement of the globes and muscle cones (decompression) results in a change in the position of the extraocular muscles and eyelid retractors. Movement of the extraocular muscles results in a change in position of the eyelid retractors. The logic of the four stage approach to surgical rehabilitation, therefore, is clear. We have been very pleased with the results when this staged approach is used.

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Familial Hiatal Hernia

To the Editor: In his letter in the November 1984 issue,[1] Dr Leung reports on a family in which six members were affected with a hiatal hernia. He goes on to observe that this may be the first recorded example of the familial occurrence of the disorder. While this may be true of the United States and Canada, it is certainly not true of the European literature.

In 1970 I published with P. Froggatt a paper[2] drawing attention to the etiologic role of heredity in hiatal hernia. In that article we undertook a comprehensive review of the world literature and reported on a family with eight unequivo-

cally affected members in three successive generations. A simple autosomal dominant inheritance due to a single abnormal gene was postulated. I have since investigated another family showing a similar mode of inheritance. In this second family there are 21 members with a hiatal hernia (all proved radiologically) in four successive generations. Apart from these high risk families, additional studies have shown that younger siblings of children with a hiatal hernia have an approximate 10% risk of being similarly affected.[3] That a hereditary factor contributes to the etiology of many cases of hiatal hernia would therefore seem irrefutable.

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Iridocyclitis Is Not Characteristic of Still's Disease

To the Editor: In his otherwise excellent review of adult Still's disease,[1] Dr Larson states, "Interestingly iridocyclitis is apparently not a problem in adults." The misleading implication is that iridocyclitis is common in children with Still's disease. It certainly is not.

The term juvenile rheumatoid arthritis (JRA) is unfortunately applied to a diverse group of diseases. In at least two subsets of patients, JRA is strongly associated with iridocyclitis. In one subset a pauciarticular arthritis develops usually between the ages of 2 and 6. This subset tends to be female, tends to develop antinuclear antibodies (ANA) and frequently develops bilateral, chronic iridocyclitis with sequelae such as band keratopathy and cataract formation.[2,3] A pauciarticular arthritis also develops in a second subset, with a later median age of onset. In this subset, test findings usually are HLA-B27 positive and ANA negative, and frequently sacroiliitis develops.[3,4] The iridocyclitis found in this subset is acute and predominates in one eye. The ocular disease is usually more benign than in the former group. Neither of these subsets have hallmarks of Still's disease, such as evanescent rash, high fever, lymphadenopathy, leukocytosis or hepatosplenomegaly.

In one survey of 668 patients with JRA, 68 patients had iridocyclitis but none of these were included in the subset of JRA characterized by rash and high fever.[4] In another series, 368 children with JRA underwent periodic eye examinations. Of the children, 66 had systemic onset disease with fevers, rash, adenopathy and visceral involvement. In none of these patients did iridocyclitis develop.[5] Finally, in a third series acute iridocyclitis was found in 2 of 36 patients with "systemic onset" JRA.[6]

By combining these three large series, one finds an incidence of iridocyclitis in juvenile Still's disease of less than 2%. In Dr Larson's review of 59 patients with adult Still's disease, an absence of iridocyclitis is not a significant deviation from the incidence in childhood disease. By contrast, iridocyclitis develops in 53% of children with ANA-positive, early-onset, pauciarticular JRA[2] and in 25% of children with pauciarticular, late-onset, HLA-B27-associated JRA when followed into adulthood.[4]

JRA is a misleading disease description. The term Still's disease for both children and adults should be reserved for a very distinct subset of patients in whom iridocyclitis is rarely found to occur despite diligent ophthalmologic surveillance.

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HLA Typing in Hashitoxic Periodic Paralysis

To the Editor: I read with great interest the letter "Thyrotoxic periodic paralysis in Navajos—HLA typing" by Williams.[1] Dr Williams has provided us with a lot of insight about HLA typing in patients with thyrotoxic periodic paralysis.

I have reported the cases of two Chinese brothers with hashitoxicosis (Graves' disease with Hashimoto's thyroiditis) evidenced by the presence of thyroid antibodies in addition to elevated thyroxine levels.[2] These two brothers also had a history of periodic paralysis. The association of familial occurrence of hashitoxicosis and periodic paralysis has not been reported before.

Recently, HLA typing was carried out on these two brothers and showed the following antigens: A2, Aw33, Bw58, Bw60, Cw3, Cw4; and Aw24, A11, Bw22, Bw60, Cw3 and Cw7, respectively. Thus these two patients share the Bw60 and Cw3 antigens in common. Further case reports are necessary to delineate the link between these antigens and hashitoxic periodic paralysis.

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Topics in Primary Care Medicine

Orthostatic Hypotension

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

Hypertension, from diagnosis to treatment, is a fairly well-defined medical entity. Hypotension is a hazier issue. There is first a considerable number of people whose low blood pressure represents but one end of a bell-shaped curve. With systolic pressures ranging from 80 to 110 mm of mercury and, without symptoms, they can be reassured of a normal if not lengthened life expectancy. At the other extreme is shock, a medical emergency characterized by pressures insufficient to perfuse vital organs. A less critical but quite common clinical problem is that of orthostatic hypotension, wherein the decline in blood pressure is elicited by the assumption of an upright posture. A practical approach to its etiology, diagnosis and treatment is presented.

Physiology

Due to gravitational forces, standing would invariably produce a decline in blood pressure and cerebral perfusion were it not for a homeostatic chain of events. Pooling of blood in the legs leads to a transient drop in cardiac output and, consequently, blood pressure. Simultaneously, however, baroreceptors in the aorta and carotid bodies sense this drop and send a message centrally. Reflex sympathetic stimulation results in cardioacceleration and both venous and arterial constriction. The augmented venous return and increased heart rate boost the cardiac output, which, combined with higher peripheral vascular resistance, returns the blood pressure towards baseline. In a normal person, this happens quickly without symptoms of major sphygmomanometric perturbations.

In actuality, minor changes can occur. With standing, the systolic pressure tends to fall, the pulse quickens and the diastolic pressure remains unchanged or rises slightly. There are, however, no agreed-upon normal limits. Averages from the literature would suggest that a drop in systolic pressure of as much as 20 mm of mercury, a decline in diastolic pressure of 10 mm of mercury and a rise in pulse rate of 20 beats per minute could be considered normal—a rule of "20-10-20." Some authors suggest that a drop of as much as 30/15 mm of mercury may be normal; however, others feel that *any* drop in diastolic pressure is abnormal. More important is the occurrence of symptoms, typically dizziness, attendant upon decreased cerebral perfusion. It is this dyad of an objective drop in blood pressure coupled with subjective light-headedness that produces the disease, orthostatic hypotension. Dizziness is the most common complaint; however, angina, blurred vision, nausea and syncope may occur. Symptoms are frequently worse in the early morning and following meals, the latter due to splanchnic diversion of blood flow.

Etiology

The major causes of orthostatic hypotension are outlined in Table 1. Patients with volume depletion often present with orthostatic hypotension and, if recognized, are the most treatable group. Hypovolemia due to gastrointestinal losses or sweating or bleeding becomes apparent on a careful history taking and physical examination. More subtle is the volume depletion stemming from mineralocorticoid deficiency. Though uncommon, Addison's disease should be considered in unexplained cases. The other major treatable cause of orthostatic hypotension is that related to drugs. Though most drugs listed in the *Physician's Desk Reference* are reported to cause dizziness, the major offenders are psychotropic and cardiovascular drugs. There are differences within categories. Among antihypertensives in common use, methyldopa, prazosin hydrochloride, clonidine and diuretics require particular caution. Among tricyclic antidepressants, imipramine hydrochloride causes frequent orthostasis, whereas nortriptyline hydrochloride may be better tolerated.

Neurologic disease usually works through a common pathway of autonomic dysfunction. In rare cases, central ner-

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vous system or spinal cord pathologic conditions, such as strokes, tumors or trauma, underlie the hypotension. More commonly, the mechanism is a peripheral neuropathy, usually diabetes, but on occasion the neuropathy of alcoholism, amyloidosis or uremia. Sometimes the autonomic system alone goes awry. Primary autonomic failure can occur as a central or preganglionic type (Shy-Drager syndrome) and a peripheral or postganglionic form. The preganglionic form has also been called multiple systems atrophy because of the eventual development of central nervous system signs such as corticospinal, cranial nerve, extrapyramidal and cerebellar abnormalities. Both this and the peripheral variant, idiopathic orthostatic hypotension, have been extensively reviewed in the literature. The rise in plasma norepinephrine levels that occurs in normal persons on standing fails to occur in cases of either multiple systems atrophy or idiopathic orthostatic hypotension. In multiple systems atrophy this is presumed due to a failure in central regulation and in idiopathic orthostatic hypotension to an actual depletion of catecholamine stores or degeneration of nerve terminals.

TABLE 1.—*Major Causes of Orthostatic Hypotension*

- Volume Depletion
  - Extrarenal losses (hemorrhage, gastrointestinal losses, sweating and so forth)
  - Mineralocorticoid deficiency (Addison's disease)
- Drugs
  - Psychotropic (tricyclics, phenothiazines, sedatives, narcotics, levodopa)
  - Cardiovascular (antihypertensives, calcium channel blockers, nitrates)
- Neurogenic
  - Peripheral neuropathy (diabetes, alcoholism, uremia, Guillain-Barré syndrome, amyloidosis and the like)
  - Primary autonomic failure
    - Central—multiple systems atrophy (Shy-Drager syndrome)
    - Peripheral—idiopathic orthostatic hypotension
  - Central nervous system or spinal cord disease (strokes, tumors, trauma)—rare
- Miscellaneous
  - Aging
  - Deconditioning (prolonged bed rest, space flight)
  - Pooling (pregnancy, varicose veins, vena caval obstruction)
  - Vasodilatation (intense exertion, heat exhaustion, fever)
  - Sympathicotonia (mitral valve prolapse, some cases of diabetes)

TABLE 2.—*Workup of Patients With Orthostatic Hypotension*

Routine Evaluation	*Additional Tests*
Document orthostasis	
Drug history	
Detect hypovolemia	
History (fluid loss, bleeding, thirst)	ACTH stimulation test
Physical factors (standing pulse increased, mucous membranes, stool Hemoccult)	
Laboratory studies (urine specific gravity and protein; blood urea nitrogen and creatinine; serum sodium and albumin)	
Assess neurologically	
Peripheral	
Physical factors (vibratory sensation, reflexes)	Nerve conduction studies
Laboratory studies (blood glucose)	Hemoglobin A_{1c} Rectal biopsy
Autonomic	
History (incontinence, impotence, anhidrosis)	Cold pressor test Plasma norepinephrine level
Physical factors (standing pulse not increased, Valsalva)	
Central	
Physical examination (corticospinal, cranial nerves, extrapyramidal, cerebellar)	Computed tomographic scan (if CNS signs on exam)
Consider miscellaneous causes	
History (aging, bedridden, exertion, heat)	
Physical factors (pregnancy, varicosities, mitral valve prolapse)	Echocardiogram

ACTH = adrenocorticotropic hormone, CNS = central nervous system

Miscellaneous causes include aging, deconditioning, pooling, vasodilatation and sympathicotonia. Among persons older than 65 years, 10% to 24% have at least a 20-mm-of-mercury drop in systolic pressure with standing. Deconditioning refers to the baroreceptor disuse that may occur in settings such as prolonged bed rest and space flight. Pooling stems from the impedance to venous return found in conditions such as pregnancy, varicose veins and vena caval obstruction. Vasodilatation that accompanies strenuous exertion, heat exhaustion and fever may produce orthostasis. Sympathicotonia is a poorly understood entity of altered autonomic function characterized by decreased parasympathetic or increased sympathetic tone, or both. This has been postulated as a cause of the orthostatic hypotension that may occur in 10% to 15% of patients with mitral valve prolapse, supported by the improvement in their orthostasis with β-blocker therapy. A similar hyperadrenergic state may produce orthostasis in certain patients with diabetes mellitus, although hypoadrenergic hypotension due to peripheral neuropathy is more common.

Diagnosis

The workup consists of documenting orthostatic hypotension, checking for treatable causes and doing a careful neurologic examination (Table 2).

Authors differ as to the best means of determining orthostatic changes in blood pressure. The pressure should probably be checked after the patient lies supine for several minutes and again after the patient stands for several minutes. Sitting is not enough, unless it produces diagnostic orthostatic changes by itself, or unless the patient is incapable of standing. Ironically, supine hypertension may be prominent, due to compensatory hormonal and volume adjustments mediated in part by the renin-angiotensin-aldosterone axis. A corollary is that before initiating therapy in a patient presumed to have hypertension, standing blood pressures should be determined.

Treatable causes are primarily volume depletion and taking drugs. Detecting hypovolemia due to gastrointestinal losses, sweating or hemorrhage is familiar to most physicians. The uncommon but readily treatable Addison's disease should be pursued with an adrenocorticotropic hormone stimulation test when the findings suggest volume depletion without an obvious cause. Drug taking will be detected by a careful history.

Third, assessing the peripheral, autonomic and central nervous systems is mandatory. Peripheral neuropathies are readily detected on physical examination or, in selected cases,

by nerve conduction studies. If present, the next step is measuring fasting and postprandial blood glucose levels. Glycosylated hemoglobin measurements or a glucose tolerance test can be used to detect less obvious cases of diabetes, although autonomic neuropathy usually occurs in a setting of long-standing, complicated disease. In a nondiabetic person, other causes of peripheral neuropathy must be considered, including alcoholism, amyloidosis and uremia.

Having excluded volume depletion, drugs or a peripheral neuropathy, we should consider a pure failure of the autonomic nervous system. Such patients may also complain of disturbances in bowel, bladder or sexual function or of decreased sweating. Indeed, impotence or incontinence may antedate the onset of orthostasis. Two bedside tests of autonomic function include the heart rate response to standing and that following the Valsalva manuever. Whereas hypovolemic patients have a reflex tachycardia on standing, those with autonomic failure are unable to raise their heart rate. Regarding the Valsalva maneuver, a normal person's pulse rate will rise during the maneuver and decline following it. The normal ratio of maximum pulse during the maneuver to minimum pulse afterwards is 1.25 or greater. A ratio of 1.0 or less is suggestive of autonomic insufficiency. A little more involved but still noninvasive procedure is the cold pressor test, wherein a patient's hand or foot is placed in an ice bath for 60 seconds; normally, the systolic pressure should rise at least 15 mm of mercury.

Should autonomic insufficiency be detected, a full neurologic examination looking for corticospinal, cranial nerve, extrapyramidal or cerebellar signs should be done. This is to separate autonomic failure of the central type (multiple systems atrophy) from the more common peripheral variant (idiopathic orthostatic hypotension). Those with central nervous system symptoms—parkinsonism being the most common—have a worse prognosis, with the average life expectancy following the onset of symptoms being seven years. The more common, purely peripheral form of autonomic neuropathy occurs in middle-aged or older patients, with a 4:1 male predominance. A computed tomographic scan of the head would be indicated primarily in the setting of abnormal findings on a neurologic examination to exclude the rare posterior fossa tumor or infarct causing orthostatic hypotension. Finally, if volume-mediated, pharmacologic and neurogenic mechanisms are excluded, miscellaneous factors such as aging, pooling, deconditioning, vasodilatation and sympathicotonia should be considered.

Treatment

Given an irreversible cause of orthostatic hypotension, therapy consists of prophylaxis, physical methods, volume expansion and vasoactive drugs.

Simple preventive measures begin with avoiding sudden standing. Once upright, flexing the calf muscles or walking to augment venous return is preferable to passive standing. Frequent, small feedings may occasionally be required, with heavier meals inducing significant blood pressure drops due to splanchnic diversion. Strenuous exertion, particularly in hot, humid weather, should be avoided.

Physical measures include elevating the head of the bed 20 to 30 cm (8 to 12 in). This activates the renin-angiotensin system resulting in compensatory volume expansion. Elastic custom-fitted garments can diminish venous pooling but may be subject to considerable variability in patient acceptance. These are not merely support hose, or even knee-high or thigh-length Jobst stockings, but rather graduated pressure garments that allow a gradient of counterpressure to be applied with maximal pressure at the ankles and slight pressure at the top.

Volume expansion begins with a liberal sodium intake of 150 mEq or more per day. Frequently, however, exogenous mineralocorticoids in the form of fludrocortisone (Florinef) acetate must be administered. The starting dose is 0.1 mg per day and may be increased by 0.1 mg per day each week up to 1.0 mg per day. The major complications include supine hypertension, edema, hypokalemia and, in a cardiac patient, congestive heart failure. The goal is not normotension. A standing systolic pressure of 80 to 90 mm of mercury is often sufficient because cerebral perfusion is maintained down to systolic pressures of 70 mm of mercury.

Although the standard of pharmacotherapy, a fludrocortisone regimen alone is frequently insufficient. Other drugs, though experimental and often disappointing, might be needed. Methylphenidate (Ritalin) hydrochloride at a dose of 10 mg one to three times a day may be tried, either alone or in cautious combination with a monoamine-oxidase inhibitor such as tranylcypromine sulfate. With these, the patient should be observed for severe hypertension in the recumbent position. Indomethacin given in doses of 25 to 50 mg three times a day meets with occasional success. Intranasal inhalation of vasopressin just before ambulating has been advocated and vasopressin has the relative advantage of a relatively brief duration of action of one to four hours. In some instances, β-blockers have been useful, particularly in sympathicotonic conditions such as mitral valve prolapse.

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How Do Doctors Discuss Do-Not-Resuscitate Orders?

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Although patient preferences are important in decisions about "do not resuscitate" (DNR) orders, little is known about how physicians discuss these orders with patients. We asked 15 physicians to simulate discussing such orders with a patient. We found a striking variation in whether physicians explicitly asked for patient preferences, how they described cardiopulmonary resuscitation (CPR) and its possible outcomes and whether they made a recommendation to the patient about DNR orders. There was no pattern to the different amounts of information presented about CPR. Physicians gave conflicting reasons for how they individualized discussions with patients. Awareness of such different behaviors may stimulate physicians to examine what they say to patients about this sensitive and important topic and why they say it.

(Miller A, Lo B: How do doctors discuss do-not-resuscitate orders? [Health Care Delivery]. West J Med 1985 Aug; 143:256-258)

Cardiopulmonary resuscitation (CPR) may not be appropriate when cardiopulmonary arrest is the expected result of a worsening clinical course. In such situations, a "do not resuscitate" (DNR) order may be indicated. Shared decision making by physicians and patients about DNR orders has been recommended in the medical literature[1,2] and by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.[3]* Little is known, however, about how physicians discuss DNR orders with patients. Physicians may find discussion about DNR orders difficult for several reasons. Some physicians may be reluctant to talk with dying patients or to share the decision-making power.[4] Other clinicians may equate talking about death with giving up or failing. Physicians may be unsure about which issues to discuss and how to discuss them. Also, they worry that discussions of limiting treatment will leave a patient with the discouraging message that "nothing more can be done."

To investigate how physicians explain CPR and DNR orders, we asked a group of physicians to simulate how they would discuss "do not resuscitate" orders with a patient who has metastatic breast cancer. The technique of simulated patient encounters has been used to study how physicians make decisions,[5] and case presentations have been used to study how they resolve ethical dilemmas.[6] We were particularly interested in how physicians describe cardiopulmonary resuscitation and its results, whether or not they make a recommendation to the patient and how they describe supportive care.

Subjects and Methods

We studied 15 general internists in the Department of Medicine at the University of California, San Francisco, School of Medicine. They were selected for their reputation for compassionate care of seriously ill patients. Ten physicians were faculty members and five were residents. One other physician was excluded from the study because he had difficulty answering the questions and felt his experience with DNR orders was limited.

One of us, a second-year medical student (A.M.), presented a standardized hypothetical case of a 65-year-old woman with carcinoma of the breast metastatic to liver, lung and bone that has progressed despite hormonal therapy and chemotherapy. Her pain was controlled with a regimen of oral analgesics, but she had progressive weakness and fatigue. She was alert and in reasonable spirits. In the past she had wanted to discuss options for her care.

The physicians were asked to speak to the interviewer and a tape recorder as if they were explaining CPR and DNR

*EDITOR'S NOTE: See also the Health Care Delivery section of the January 1984 issue of *WJM*: M. R. Levy, MD, M. E. Lambe, MD, and C. L. Shear, DrPH: "Do-Not-Resuscitate Orders in a County Hospital," pp 111-113; R. F. Uhlmann, MD, W. J. McDonald, MD, and T. S. Inui, MD: "Epidemiology of No-Code Orders in an Academic Hospital," pp 114-116, and M. A. Lee, MD, and C. K. Cassel, MD: "The Ethical and Legal Framework for the Decision Not to Resuscitate," pp 117-122.

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ABBREVIATIONS USED IN TEXT
CPR = cardiopulmonary resuscitation
DNR = do-not-resuscitate

orders to the patient. The interviewer did not simulate patient questions or responses. After the simulated discussion, the interviewer asked standard questions about what the physician usually said in discussing DNR orders with patients.

Although there was wide variation in individual responses, there was no systematic difference between residents and faculty. Therefore, we have combined our results for faculty and residents, except as noted. Similarly, because there was no systematic difference between simulated discussions and responses to direct questions, we have combined data from these two sources.

Results

All physicians asked the "patient" to participate in the decision about CPR. In all, 11 (73%) asked explicitly what care she wanted if her heart or lungs were to stop. The remaining physicians posed the issue indirectly by asking the patient for her wishes if she became "very ill" or "something catastrophic" happened. All physicians but one summarized the prior clinical course with the patient to put the discussion of DNR orders in context.

Twelve physicians (80%) described CPR, but their descriptions varied. All 12 described intubation, but only 6 mentioned chest compression and only one electroshock. Some of the physicians explained why they do not describe some aspects of CPR. Two said that most patients know what CPR is because it is portrayed on television. Another feared that describing CPR would frighten the patient.

Three physicians (all faculty) did not describe CPR. When asked if he describes it, one responded, "Are you kidding? Patients have enough things to worry about. They've got death to worry about and not our particular version of technocratic death."

Ten physicians (67%) described the possible outcomes of CPR, but again they varied in what they specifically mentioned. Eight physicians described intensive care, five mentioned death explicitly, four said that there would be no change in the underlying illness after successful CPR, three mentioned possible brain damage and two spoke of a prolonged stay in hospital. One physician mentioned intensive care because the patient might be frightened by being in the intensive care unit, but he did not mention brain damage because the patient would not be aware of it. When asked if she mentioned possible brain damage after CPR, another physician said, "That's a good thought. It's so common afterwards, but I don't think I have [mentioned it]." Physicians disagreed whether or not to mention death explicitly: 11 did not; of these, 5 believed it was clear to the patient from the context of the discussion that a person would die without CPR.

Eleven physicians (73%) tailored the description of CPR to fit the patient and her situation. Explanations of how to individualize discussions varied greatly. Three physicians would give *more* details about CPR if the patient indicated that she wanted CPR, to be sure that the patient understood what is involved. Conversely, two other physicians would give *less* description if the patient wanted CPR. One was reluctant to precipitate an overt disagreement with the patient, and the other did not want to appear to dissuade the patient from her preferences. Two doctors would give more details if they believed CPR would not be effective. Another physician would limit the description with patients who deny the situation or have trouble making the decision.

Seven physicians (47%) recognized that their presentation might be biased. One physician said that she usually has decided what is appropriate before she discusses DNR orders with the patient. If she feels that CPR is not indicated, she "stacks the cards" to favor that decision. Another physician described the process as "explaining to the patient what you want and getting the patient to ask for what you want." They worried that patients might insist on CPR against their judgment as physicians. One described the dilemma and his ambivalence:

> I have two biases. One is that the patient needs to be the one to make the decision as long as she's with the program. But interlaced with that is that if there is no hope, then I don't feel that I'm obliged to treat in a hopeless situation. And I'll usually let the patient override that, if the patient is with it. But I'd rather the patient agreed to a "no code." I try not to make my opinion known, so that the patient's decision is informed. But I think I may bias it by making CPR sound as gruesome as it really is. I don't think CPR is pleasant and wouldn't want my wife or parent to have it.

Seven physicians (47%) gave a recommendation to the patient about CPR. One physician explained that the patient depends on the physician's opinion, "just like you'd depend on a car mechanic. . . . But I make it clear that we'll follow the patient's wishes because it's her death." Another physician made clear recommendations, while giving the patient a choice, "My feeling about it is that, given that we can't do much about your breast cancer, we should just make you comfortable if you stop breathing or your heart stops. . . . We wanted to discuss this issue with you and see what your feelings and thoughts about this are." Another physician emphasized supportive care in giving his recommendation: "I think what we should do right now is concentrate on the things we can treat."

Supportive care was mentioned by all physicians during discussions of CPR. One physician emphasized the importance of making the discussion positive rather than sounding as if "I am withholding CPR from you." Specific types of supportive care mentioned were controlling pain, seeing the patient regularly, arranging for visiting nurses and other home care, letting the patient cry and holding the patient's hand. One physician gave the patient her home phone number and said that the patient would probably need to see her more frequently now. Four physicians said explicitly that further care would not be affected by the patient's decision about CPR.

In the simulated discussions, physicians used medical jargon that might not be understood by patients. Such phrases included "big intravenous lines," "oxygen exchange" and "something acutely happened." Other phrases used were general and possibly ambiguous, such as "heroic," "catastrophic," "sophisticated," "cardiac problems" or "respiratory distress."

Discussion

Mutual decisions by physicians and patients have become the ideal for medical decision making. In such shared decision

making, patients must be informed about and understand the nature of their illness, the proposed treatment, the likely outcomes and the alternatives.[3] We found striking variation in discussions with the patient about CPR. Descriptions of CPR and its outcomes varied greatly: almost all physicians mentioned intubation, whereas only two mentioned a long hospital stay. Given such variability, patients may not receive enough information about CPR to enable them to make an informed decision.

There was no consistent pattern regarding different information presented about CPR. For example, some physicians give more details when a patient favors CPR, whereas other physicians give more details when a patient is against CPR. Such discrepancies suggest that it may be helpful for physicians to analyze what they say about CPR and why they say it.

Physicians in this study realized that they can influence patient choices. Some acknowledged that their presentations made it difficult for the patients not to agree with DNR orders. They justified such influence by their belief that CPR was not medically indicated. However, apparently technical judgments that CPR is "futile" or that a case is "hopeless" may be confounded by a physician's implicit assumptions and values, which may differ from those of the patient.[7] One way to minimize the effect of such assumptions is to conduct rigorous studies of patient outcomes after CPR.[8] These studies may identify clinical situations in which CPR is ineffective and therefore need not be offered to a patient as a therapeutic option.

Other physicians in this study hesitated to make recommendations about CPR. They wanted to be sure the patient had a choice and feared they would impose their wishes on her. However, some patients want the physician to make a recommendation, rather than merely describing alternatives.[9] Moreover, a completely objective presentation is impossible, since assumptions and values cannot be avoided. One approach in making recommendations to patients may be for physicians to be aware of their biases and to state them explicitly, like the physician who said that he believed that relief of symptoms was the most appropriate goal of treatment.

Supportive care was considered an important topic in discussions about DNR decisions. Physicians feared that discussions of limiting care could cause patients to feel abandoned or to believe nothing more could be done. Several physicians emphasized that although the explicit purpose of the discussion was to learn the patient's wishes about CPR, a more important implicit purpose was to communicate caring and concern to the patient.

Our study has several limitations. The number of physicians studied is small, and our results may not hold for physicians in other clinical settings, such as nonteaching hospitals and physicians other than internists. The format of a simulated noninteractive discussion is artificial. It is not known how performance in this situation correlates with performance with actual patients. Some physicians may have spoken more technically to a medical student than they would have to a layperson. However, it is unlikely that physicians merely gave responses that they considered to be socially acceptable, since they made candid responses and unsolicited comments.

Several physicians spontaneously remarked that they had found participating in the study to be helpful. One physician commented that his training had given little attention to talking with terminally ill patients. "I had no idea what I was doing when I started. No one talked to me about all this; I just had to wing it. Now I know what sells, and that's what I do." Another physician said that he had never previously thought about what he said to patients concerning CPR and that the simulated case helped him to examine what he says.

We hope that this initial study will stimulate physicians and medical students to examine what they say to dying patients and to consider how their words affect their patients. Simulated discussions between physicians and dying patients may be a useful educational technique to improve the care of such patients.

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Special Article

Low Back Pain

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Low back pain is one of the most common and costly afflictions of our society. The majority of adults will have at least one episode of acute low back pain that will likely resolve regardless of treatment. Lumbar spine radiographs are overused and there is little scientific support for many of the therapeutic interventions advocated. Even for those patients with symptomatic herniated disc, only a small fraction will ultimately require surgical intervention.

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Low back pain (LBP) is a problem frequently encountered by primary care and emergency room physicians. In the National Ambulatory Medical Care Survey, LBP was the number one symptomatic complaint expressed by patients 25 to 60 years old seeing office-based physicians,[1] and it is the most costly medical problem in our society for the age group 30 to 60 years.[2] Poor understanding of this common syndrome leads to overuse of resources and the prescription of poorly validated treatment methods. In this review I will cover those aspects of LBP that are germane to an internist's practice and will discuss surgical intervention only as it pertains to decision-making about referral.

Epidemiology

LBP is the most common cause of limitation of activity for those under 45 years of age and is surpassed only by heart disease, arthritis and rheumatism in the age group 45 to 64 years.[3] In all, 60% to 80% of the population will experience at least one episode of acute back pain,[4-6] and a prolapsed disc is second only to schizophrenia as the most frequent condition for which disability payment is allowed by the Social Security Administration in those under 40 years of age.[7]

LBP represents a major issue for industry, where it is second only to upper respiratory illness in accounting for lost time from work—93 million days annually.[8] In the state of Oregon, the back was the injured body part in 31% of all claims accepted by Workers' Compensation, a frequency 2.5 times greater than that of any other body area.[9] Of such injuries, 75% involve the age group 20 to 44 years and the average amount of time lost from work is 14 days.

Vocational factors implicated in workplace-related back pain include physically heavy work, static work positions such as sitting and driving, frequent bending and twisting, lifting and forceful movements, repetitive work and vibration.[8,10,11] At the Kodak Company, back pain developed in 35% of sedentary workers and 47% of manual material handlers, with only 15% of cases being related to a definite injury.[12]

Biomechanics

The lumbar spine consists of a series of motion units each having an anterior and posterior segment. The anterior segment, composed of two vertebral bodies and the intervertebral disc, bears weight and absorbs shock.[4] The posterior segment, consisting of the vertebral arches, transverse and spinous processes and the inferior and superior articular facets, protects the neural structures and directs movement of the unit in flexion and extension. The disc is composed of the nucleus pulposus and a circumferential, intertwining fibroelastic mesh, the annulus fibrosus, which attaches to the vertebral bodies and permits a rocker motion. The unit is stabilized by a series of ligaments that minimize shearing forces and the paravertebral muscle bundles that provide balance for the static spine and strength for the kinetic spine.

Several factors relate to the stress on the motion unit. Disc pressure reflects the response to shearing and rotational loads, abdominal cavity pressure supports the trunk anteriorly and the myoelectric back muscle activity balances the gravitational forces in upright posture and forward flexion. Using intradiscal pressure measurements, Nachemson has shown marked variations in forces in various positions and activities.[13,14] For example, when a person is lying supine in the semi-Fowler position, a force of 100 Newtons is exerted on the L-3 disc. A person sitting upright without support generates seven times this force and when the same person bends forward and rotates while holding a 10-kg weight, the force increases 20-fold.

Causes of Low Back Pain

Though most patients experiencing LBP will have benign, nonemergent mechanical problems for which specific diagnoses will not be made, it is imperative to consider other

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Reprints are not available.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
HNP = herniated nucleus pulposus
LBP = low back pain

disorders that may appear to be back pain. These may be classified as infectious (pyogenic osteomyelitis, epidural abscess), inflammatory (spondyloarthropathy), metabolic (osteoporosis, osteomalacia, Paget's disease), neoplastic (metastatic, primary cord tumor) and visceral (abdominal aortic aneurysm, urinary tract infection, pancreatic disease).[15,16] It is not within the scope of this review to address every potential cause of back pain, but selective entities representing common problems or areas of confusion are highlighted below.

Intervertebral Disc Disease

Though most structures in the back have been assigned roles in the causation of back pain, the disc has been implicated, at least indirectly, as the primary agent. Among reasons are the observations that true herniation is preceded by attacks of back pain, intradiscal injection reproduces pain and the anatomic changes in the disc and annular ruptures are first seen at younger ages, the same time that LBP becomes a clinical problem.[17]

At autopsy, herniated nucleus pulposus (HNP) is seen in 15% to 30% of specimens and degenerative changes are observed in the motion segments of all persons over the age of 60 years.[18,19] With age, the meshwork of the annulus becomes fibrotic, lessening the recoil properties of the hydraulic mechanism. These changes, coupled with microscopic fracturing of the end plates and facets, reduce the overall torsional strength of the unit and its capacity to absorb energy. Although pain produced by true herniation impinging on the nerve root is easily understood, the role of the changing mechanical behavior of the disc, the alteration of the height and protrusion of the disc on other sensitive tissues is not well defined vis-à-vis LBP. These age-related degenerative changes are often present in the absence of LBP.

HNP is generally a disorder of younger people, most frequently involving the L5-S1 and L4-5 discs.[20,21] The classic syndrome contains the following features: leg pain is dominant, unilateral and in a sciatic distribution, often aggravated by coughing, sneezing and forward flexion; paresthesias are localized to a dermatomal distribution; positive tension signs are present, including straight-leg raising, crossed-straight-leg raising and bowstring; at least two neurologic signs are demonstrable, including muscle wasting, motor weakness, diminished sensation and diminished reflex, and a contrast study will be positive for disc herniation at a level corresponding to the clinical features.[22] Table 1 lists the findings in the three commonly encountered disc syndromes.

TABLE 1.—*Root Compression Syndromes*

L5-S1 Disc (S1 Root)
- A. Pain/numbness—Posterior thigh and leg; posterolateral foot, lateral toes
- B. Weakness/atrophy—Plantar flexion foot, toes decreased; atrophy posterior compartment
- C. Reflex—Depressed Achilles' reflex

L4-5 Disc (L5 Root)
- A. Pain/numbness—Posterior thigh, anterolateral leg, medial foot and great toe
- B. Weakness/atrophy—Dorsiflexion foot, toes decreased; atrophy anterior compartment
- C. Reflex—No change

L3-4 Disc (L4 Root)
- A. Pain/numbness—Posterolateral aspect thigh, across patella, anteromedial leg
- B. Weakness/atrophy—Knee extension weak; quadriceps atrophy
- C. Reflex—Depressed patellar reflex

Several pitfalls are inherent in the diagnosis of HNP. Other disorders may mimic some of the above features, and the straight-leg raising test, or one of its variants, manifested by radicular leg (not back) pain upon passive stretching of the sciatic nerve, is not specific to HNP. Though virtually all patients under age 30 with a symptomatic herniation will have a positive straight-leg raising (true-positive) test result, the majority of patients with a positive test do not have a disc herniation (false-positive).[21] Additionally, older patients with confirmed herniation or those with higher root lesions (above L5 root) may have negative straight-leg raising test results (false-negative). The neurologic findings should be used as guidelines only in identifying the level of involvement, because overlap in innervation may lead to misinterpretation. The sensory examination must be mapped carefully to distinguish dermatomal from nondermatomal impairments.

Ankylosing Spondylitis

Ankylosing spondylitis, an inflammatory arthropathy with a strong predominance in men, has an age distribution similar to that of HNP and mechanical LBP.[23] Suggestive historical features are an age of onset of less than 40 years, insidious onset, duration longer than three months, morning stiffness and improvement with exercise. Positive responses to four of these features have a 95% sensitivity and 85% sensitivity for the disease.[24] A past history of iritis would further heighten suspicion. Maneuvers to assess spinal mobility, chest expansion and sacroiliac joint tenderness may be useful,[25] though in a recent series these tests did not have any clinical value in helping to distinguish between ankylosing spondylitis and noninflammatory back disorders.[26] The diagnosis is confirmed by plain radiographs of the sacroiliac joints that show bilateral sclerosis. In most instances, a single anteroposterior view of the pelvis will demonstrate the abnormalities by the time the patient first seeks medical attention. Nuclide scintigraphy and computed tomography have been reported to be useful in reaching a diagnosis in suspected cases when plain films are not yet abnormal, but their operating characteristics remain to be defined. Though results of the human leukocyte antigen B27 study are positive in 90% of white Americans with primary ankylosing spondylitis, the test does not confirm or exclude the presence of the syndrome, the diagnosis of which must be based on radiographic findings.[27] Exercises and anti-inflammatory drugs are the mainstays of therapy.

Facet Arthropathy

The lumbar zygapophyseal (facet) joints, located posterior to the plane of the intertransverse ligament and innervated by the dorsal primary ramus of the spinal nerve, have been

implicated as a common cause of LBP that mimics HNP.[28] The pain in this syndrome is intermittent, exacerbated by extremes of sudden movement and associated with diffuse thigh pain, often terminating at the knee. Physical findings are limited to tenderness over the facet joints magnified by hyperextension. Intraarticular facet block done with fluoroscopic guidance may confirm the diagnosis and injection may provide relief in selected patients.[29,30]

Spinal Stenosis

The term spinal stenosis includes narrowing of the spinal canal, nerve root canals and intervertebral foramina, all of which cause nerve root entrapment.[31] All forms of stenosis are characterized by a shallow lateral recess, that area bordered anteriorly by the vertebral body, laterally by the pedicle and posteriorly by the superior articular facet.[32] Those with the spinal stenosis syndrome experience back pain, transient motor deficits, tingling and intermittent pain in one or both legs, worsened by standing or walking (neurogenic claudication) and relieved by sitting or squatting, in contradistinction to HNP. Objective neurologic signs are absent at rest but may be present upon examination after exercise.[33,34] The diagnosis may be confirmed by a computed tomographic (CT) scan and, in some patients, symptoms may be relieved by surgical correction.[34,35]

Myofascial Syndromes

Myofascial pain syndromes arise from trigger points, focal areas of hyperirritability located in skeletal muscle and fascia which, when palpated, produce referred pain to distant sites.[36] The characteristics of trigger points have been delineated and the resultant syndromes causing LBP, including the quadratus lumborum, iliolumbar and piriformis syndromes, have been described.[37-41] Pain and weakness are elicited by maneuvers that cause the involved muscle to contract. Effective treatment may result from application of vapocoolant spray, injection of local anesthetic into the trigger point or ischemic compression of the area.[36]

Fibrositis, a related and common form of nonarticular rheumatism, is characterized by ill-defined musculoskeletal pain—often worsened by stress, cold and exercise—depression, nonrestorative sleep, chronic fatigue and early morning stiffness, and a physical examination will show no abnormalities except for tender spots located over muscles and ligamentous bony insertions.[42,43] The cause of the syndrome is unknown and its effective treatment is difficult. Antidepressants, centrally acting muscle relaxants and local injections may be of benefit.

Clinical Evaluation

The evaluation of LBP focuses on the differential diagnosis discussed above. Known malignancy, a history of intravenous drug abuse and constitutional symptoms such as anorexia, weight loss and fevers suggest metastatic cancer, vertebral osteomyelitis or epidural abscess. Inquiry about other organ-specific symptoms may uncover a nonmechanical cause of LBP, particularly urinary tract infection.[16] Age greater than 60 years and corticosteroid use have associated osteopenia and resultant compression fractures as a cause of LBP. The character of the pain pattern may suggest one of the syndromes discussed above, and bowel, bladder or sexual dysfunction may be clues to central midline disc herniation, carcinomatous extradural cord compression or cord tumor. A past history of LBP and related interventions, disabilities and litigation aid in placing the problem in perspective and planning a management strategy.

The physical examination should include observation of gait, trunk mobility and deformities and inequality of leg lengths.[21] In addition to a detailed neuromuscular examination, abdominal and vascular evaluations should be included, particularly in the elderly and those with symptoms suggesting neurogenic claudication. Localization of trigger points may lead to immediate therapeutic intervention.

Lumbar Spine Radiography

LBP is the most frequent symptom leading to diagnostic roentgenograms in an ambulatory care setting, with an estimated 7 million films done annually in the United States at a cost of $350 to $500 million.[44,45] Lumbosacral radiography is the largest contributor to gonadal irradiation and, unfortunately, the majority of specific findings (osteophytes, narrowed disc space, spondylolisthesis) do not correlate with the presence of LBP or predict its cause.[46] LaRocca and Macnab showed that only 7% of 150 asymptomatic laborers over the age of 35 years had normal radiographs and that the prevalence of degenerative changes (84%), congenital anatomic variations (64%) or both (57%) was comparable to a similar group with LBP.[47]

Liang and Komaroff, applying a formal decision analysis, compared a strategy that included radiographs on the first visit for acute, uncomplicated LBP with one in which films were delayed four to eight weeks.[48] Using prior probabilities of diseases causing LBP that could be diagnosed radiographically (disc space infection, osteomyelitis) and for which a specific treatment was available, the former strategy led to a decrease in suffering of only 58 minutes while generating a tenfold increase in cost and radiation exposure. Clinical studies have confirmed the conclusion that lumbosacral spine roentgenograms are of negligible diagnostic value in otherwise healthy patients with LBP under age 60 unless major direct spinal trauma, malignancy or infection is a concern or the pain has persisted for more than six to eight weeks.[16,44,49,50] The benefit of having oblique lumbar radiographs in addition to a single frontal and lateral view is negligible.[44,45]

Management of Acute LBP

Acute LBP is a self-limited disorder, with 50% of patients pain-free by one week, 80% by two weeks and 90% by eight weeks regardless of therapy.[51] Although innumerable therapeutic modalities have been advocated, the rate of spontaneous resolution, the diverse causes of LBP and the difficulty in measuring the symptom, pain, represent problems in evaluating efficacy of a given therapy.[52-54] Deyo has recently reviewed these methodologic pitfalls.[55]

The supine position maintained during bed rest has a theoretical advantage for instances of disc protrusion, considering disc pressure measurements discussed above.[14] Whether bed rest is useful in other causes of LBP is even less clear. Bed rest for 7 to 14 days, using a firm mattress and keeping hips and knees flexed, is an appropriate trial, acknowledging that the recommendations for duration are entirely empirical.[21,56]

Bathroom privileges should be allowed since the contortions associated with use of a bed pan are discouraging and biomechanically counterproductive. Lifting, bending and prolonged sitting should be avoided.

Because postulated mechanisms for LBP of soft tissue or disc origin implicate an inflammatory response, an anti-inflammatory agent is recommended. None of the nonsteroidal anti-inflammatory drugs has been shown to be more effective than aspirin and all are more expensive.[21,51,55,57,58] Antispasmodics and muscle relaxants probably act more by a sedative effect than at a specific neuromuscular site, are expensive and, again, none has been shown to be clearly efficacious.[59-65]

In addition to aspirin in therapeutic doses and bed rest, we recommend local heat, using a moist, hot towel, or cold applications, using a small wet towel placed in the freezer until malleable; these are simple adjuncts having theoretical support.[66-68] The traditional traction apparatus using small weights does little more than keep the patient in bed, because it has been shown that at least 25% of body weight must be applied to even begin to lower intradiscal pressure.[21,51,55] Spinal manipulation, of which several methods are used, has also not been proved to be effective.[21,69-71] Most important is reassuring the patient that LBP is generally self-limited and the prognosis for return to usual activities is good.

Surgical Procedures

Failure of a conservative therapeutic program for acute back pain frequently leads primary care providers to consider orthopedic or neurosurgical referral. Unfortunately, expectations of the referring physician and patient are often unrealistic with respect to the success of surgical treatment for symptomatic HNP. Though details of various surgical procedures for the lumbar spine are not germane to this review, an understanding of the natural history of conservatively treated and surgically treated disc disease is important.

In general, acute cauda equina syndrome and major or progressive paralysis represent clear indications for surgical intervention.[21] Other indications are relative, and patient selection remains a most important determinant of outcome of surgical therapy.[21,72,73] Operative procedures should be reserved for patients with symptoms of sciatica and neurological findings on examination, who have continued problems after 6 to 12 weeks of conservative therapy.[21,74] The goals of operations for HNP are to relieve sciatic and low back pain and to improve physiologic function, employment status, social functioning and the ability to perform activities of daily living.[21] The younger the patient and the greater the degree of herniation seen during the surgical procedure, the more likely it is that the pain will be relieved. Complete relief of back and sciatic pain occurs in approximately 60% of operative patients, with sciatic pain being relieved more frequently than back pain.[75] However, long-term follow-up of patients with sciatica and neurological findings who did not undergo surgical procedures showed that 52% were without symptoms and an additional 27% had only mild symptoms.[76] Work capacity and activity restriction were also similar in surgically versus conservatively treated groups.[76] Additionally, up to 10% of patients having operations for classic, severe sciatica will have a negative exploration.[75] This group has the worst prognosis. In general, only about 20% of patients with herniated nucleus pulposus require surgical intervention.[21] Indications for chymopapain injection are similar to those for surgical intervention.[22,77-79] Response to injection may not be complete for up to six weeks, and failure of chymopapain therapy does not obviate a subsequent operation. The referring physician, surgeon and patient must discuss the expectations of surgical intervention and the limitations and risks of the planned procedure.[80]

Diagnostic Studies

If it is agreed that an operation should be offered to and accepted by the patient, further diagnostic studies are indicated, remembering that up to 30% of asymptomatic persons have myelographically proved disc herniations.[72,81] It is important to do further studies because the correlation between the predicted level of herniation based upon neurological deficits on examination and the level of herniation on study is only 50% to 60%.

Much controversy exists today as to whether metrizamide myelography or computed tomography is the method of choice to establish the diagnosis and location of lumbar disc herniation.[82] Myelography permits direct visualization of the lumbar and sacral nerve rootlets. It is often difficult, however, for the myelographer to distinguish between a bulging disc, which does not cause nerve root compression, and a herniated disc. Also, symptomatic lateral herniations, particularly at the L5-S1 level, may be missed with myelography.[83,84]

With high-resolution CT scanners, a noninvasive diagnosis of HNP is possible. In series comparing CT with myelography in evaluating HNP in patients who underwent surgical exploration, CT has been shown to be of equal accuracy.[84,85] CT is particularly useful in evaluation of the vertebral bodies, posterior elements and paravertebral soft tissue mass and is the most precise method for assessing spinal stenosis. Also, CT is more accurate in detecting lateral herniations.[84] However, other extradural processes, such as scars, masses and spondylosis, may mimic focal disc protrusion and, as in myelography, it may be difficult to distinguish true herniation from a bulging disc.

Presently, the choice of initial diagnostic method for evaluation of HNP remains one of opinion. Review of the clinical information with the radiological and surgical consultants is important in determining a diagnostic strategy. An unequivocally abnormal or unequivocally normal CT scan may obviate the need for myelography unless the clinical evaluation contradicts the CT findings.[84] If neither the CT scan nor the myelogram provide a satisfactory answer, CT and metrizamide myelography done concomitantly may give additional clarification of the anatomy.

In difficult situations where a strong functional component appears to be present in patients with symptoms and signs suggesting nerve root compression, differential spinal anesthesia may be useful. This procedure consists of an injection of saline followed by injection of increasing concentrations of procaine hydrochloride into the subarachnoid space, causing sympathetic, sensory and motor blockage. If pain is relieved with saline or not relieved despite administration of 1% procaine hydrochloride, a strong psychological component to the pain problem is suggested.[21]

Management of Chronic LBP

The management of a patient with chronic LBP is often a vexing problem for physicians.[86] These patients often fall into

the category of "undesirable," arousing animosity in, and the use of pejorative terms by, their physicians. As in other nonmalignant chronic pain syndromes, narcotic analgesics are to be avoided and alternative therapeutic modalities have been used, including biofeedback, acupuncture, transcutaneous nerve stimulation, implanted neurostimulators and ablative neurosurgical procedures, all with varying success and all fraught with methodologic problems.[55] For selected patients, trigger-point injections may provide relief. In smaller subsets of patients, epidural corticosteroids[87-89] and corsets or braces[21,51,55] may be beneficial.

For most patients, however, there is little specific that one can offer. Although psychological profiling may be of some use in predicting responses to surgical intervention,[90,91] it is counterproductive to attempt to assign patients to organic or psychogenic categories.[86,91,92] In contradistinction to the disease model, the learning model, in which illness is comprised primarily of behavior and chronicity insures the need for behavior change, provides a more rational view of the chronic pain syndrome.[93] It can be assumed that the longer the patient has pain, the more the psychological factors become important in influencing neurophysiologic mechanisms underlying pain behavior. In this context, symptoms are to the disease model as behavior is to the learning model. Using scales of reliability such as the Minnesota Multiphasic Personality Inventory does not help to distinguish patients with organic or psychological pain. Both groups have increased scores for hypochondriasis, depression and hysteria indistinguishable from those of psychoneurotic patients.[86] These observations underscore the point that it matters little whether or not pain is real, but identifying those factors that influence pain is critical. The concept of chronic pain programs utilizes the principles of behavior modification, with goals being to identify and eliminate positive reinforcers for pain behavior, increase physical activity and decrease drug usage. These programs require commitment and motivation on the part of the patient and family and considerable financial expenditure. The long-term results of such programs vary.[94,95]

For most patients with chronic LBP, education and an exercise program are the foundations of successful therapy. Exercises, which may begin after the acute exacerbation abates, aim to minimize lumbar lordosis, thereby decreasing subluxation of the overriding facet joints, to decrease shearing stresses, to widen the intervertebral foramina and to strengthen abdominal and spinal musculature. Several types have been advocated, including extension and lumbar isometric flexion exercises, but no single program has clear superiority over another.[4,96-98] One of the most successful and widely available back programs is the Young Men's Christian Association's Healthy Back Program.[99] This course, offered throughout the United States, consists of six weeks of twice-a-week sessions, each of which include relaxation exercises and an increasing sequence of limbering, strengthening and stretching exercises. The charge is nominal, and the skills learned are continued at home indefinitely to minimize chronic pain and prevent acute attacks of LBP. The details have recently been published in an inexpensive book.[100]

Disability

Because LBP is such an important malady in the workplace, the issues of disability and compensation frequently arise.[101] The statutory definitions of a compensable personal injury are that it was out of, and in the course of, employment and occurred accidentally.[102] In most cases, physicians have no role in these decisions except in clear instances of extreme force or overt trauma, a small fraction of the occupationally related LBP. A physician may attend to the degree and nature of the impairment—that is, an objective assessment of anatomical or functional loss. However, there are often no objective means by which to assess many forms of impairment, particularly in LBP, and to establish the point at which healing is complete.[103] Disability, the loss of capacity to engage in gainful employment owing to the impairment, is in large measure behavioral and its determination is an administrative decision.[103-105] Hadler has reviewed the major points of interpretation of Workers' Compensation Law as related to LBP.[102]

Prevention

Given the staggering costs in dollars and reduced productivity resulting from LBP, prevention must be a major focus. Pre-employment screening by x-ray studies is not useful for identifying workers at high risk.[106,107] A history of prior LBP, however, and inability to demonstrate an isometric lifting strength equal to that required for a worker's job may have greater predictive value.[108-110] The study of ergonomics, the science of energy utilization in the workplace, has led to recommendations that minimize risk of back injury, including use of substitution devices, such as hoists, cranes and dollies, improved equipment and task designs to decrease vibration and stress and variation of work practices.[111] These principles have also been incorporated into car seats, furniture and leisure-time equipment design.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Percutaneous Transluminal Coronary Angioplasty

QUESTION:

Is Percutaneous Transluminal Coronary Angioplasty (PTCA) considered accepted medical treatment?

OPINION:

In the opinion of the Scientific Advisory Panels on Chest Diseases, Internal Medicine and Radiology, single vessel and multi-vessel percutaneous transluminal coronary angioplasty (PTCA) is considered established medical practice for patients who have coronary artery atherosclerosis.

PTCA should be done on carefully selected patients by physicians specially trained in the procedure and in facilities where the training of the PTCA team has been approved by medical staff or other peer reviewers. A cardiac surgery team should be immediately available in facilities where PTCA is done, in the event of complications.

Open-Heart Surgery— An American Experience in Shanghai

ELIAS S. HANNA, MD; SAMI S. KABBANI, MD, *and* TALI T. BASHOUR, MD, *San Francisco*

It was a first in more than one way—the first time a foreign medical team was allowed to operate in Shanghai, the first time a coronary bypass operation was done in Shanghai and the first time an important Chinese official was operated on by foreign doctors on Chinese soil.

For our team, however, operating in a foreign country lagging behind in modern medical technology was not exactly a new experience. Established in 1974 by Elias S. Hanna, MD (presently Chief of the Department of Cardiac Surgery and Medical Director of the newly formed Western Heart Institute at St Mary's Hospital and Medical Center, San Francisco), the Hanna Foundation has, over the past six years, sponsored special medical trips to many Third World countries, including Taiwan, Sri Lanka, Iraq and Syria. The traveling medical team usually included two cardiovascular surgeons, two cardiologists, one anesthesiologist, one perfusionist, one respiratory therapist, one operating room nurse, one intensive care nurse, one catheterization laboratory technician and one biomedical engineer.

On each of these trips the American team worked closely with a counterpart team from the host country (usually in a university setting) for a period of two to three weeks, doing cardiac catheterizations and operating on 5 to 12 local patients with a variety of heart disorders, introducing as a by-product the latest methods related to the management of heart disease to the foreign land. The China trip was the latest of the Hanna team's ventures.

The idea of visiting China developed in September 1980 at the annual meeting of the International College of Surgeons and through correspondence with professors of surgery at the Shanghai Second Medical College. Approval for the trip had to be cleared through the proper Chinese authorities, and it was not until September 1981 that the final details of the trip were worked out.

The tour was to be arranged and the tour guides provided by the Chinese Youth Federation, which has the official function of handling group trips to mainland China and maintains an office in Hong Kong. The original plan called for working in three hospitals affiliated with the Shanghai Second Medical College, but the number was reduced to two for logistical reasons.

The scientific exchange program with the People's Republic of China has so far resulted in two trips of the heart team to China (October 1982 and October 1983), and a six-week visit was made by the Chinese cardiovascular surgical team to St Mary's Hospital and Medical Center as guests of the Western Heart Institute.

The 1982 Visit

We arrived in Shanghai, the most populated city in China (12 million), on the eve of October 31, 1982, and were well received at the airport by the Chinese officials.

In Shanghai we stayed at the Jing-Jiang, an old hotel that dates back to "colonial time," but which is still considered one of the best hotels in China. The hotel was modest by western standards. On the way to the hotel, we were given our first instructions by David, our tour guide whom we soon got to like very much: "Don't drink running water," he suggested. "Instead, drink Chinese tea." As though to prove his point, Chinese tea was available in each hotel room, served with every meal and was an essential part of conferences, discussions and work breaks. Chinese tea, we were told, "reduces weight" and "prevents cancer"! David went on: "Don't go out at night." "Don't use local Chinese money," but rather the "special paper money" obtainable at the hotel exchange desk and at special "friendship" stores attended by foreigners.

We left the hotel for an early morning stroll and were amazed at the sight of dozens of Chinese (mostly elderly) performing the classic Chinese sport, *Tai-Chi Chuan,* commonly known in the West as "shadow-boxing." It appeared to be a blend of Swedish exercises, karate movements and Indian yoga. We were told that the sport dates back to 500 AD and is still practiced by most Chinese. Besides helping persons attain a "healthier body and spirit," it is supposed to "cure" many chronic conditions such as hypertension, tuberculosis and paralysis.

Chinese dress was modest and clean but monotonous. Almost all men and women wore blue jackets and grey or blue pants. The people seemed healthy. Rarely did we encounter an obese person, and seldom did we notice bad teeth. They

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seemed quite adjusted to order (waiting lines were commonplace) and minded their own business. Seldom were we considered a novelty, and never were we followed by crowds.

The first day (November 1) was spent visiting the Shanghai Second Medical College and the five hospitals affiliated with it. There are two western-style medical colleges in Shanghai and a third college confined to teaching traditional Chinese medicine.

After 1981 the Second Medical College went back to a six-year program. (This had been reduced to five during the Cultural Revolution of 1966 to 1973.) The Second Medical College hosts 3,500 medical students (about 500 per year) and has three-year postgraduate courses in all specialties (100 postgraduates a year), leading to a master's degree. Recently, a doctorate (PhD) degree has been added in some of the programs.

Affiliated to the Shanghai Second Medical College are five general hospitals: (1) Rui-Jin, 1,200 beds (general); (2) Third People's Hospital, 650 beds (general); (3) Xin-Hua Hospital, 600 beds (mostly pediatric); (4) Ninth People's Hospital, 500 beds (mostly dentistry), and (5) Bao Gang Hospital, 300 beds (mainly industrial injuries). During 1981, the five hospitals combined treated about 50,000 inpatients and 4,500,000 outpatients.

After a reception and tea session with the President of the University (Professor Lan Xi-Ch'un), we visited the first three hospitals, but later our work was confined to the first two.

We learned that in 1956 the first open-heart procedure was done in China under hypothermia. The Chinese then developed their own extracorporeal machine (the most recent being Shanghai Type III) and their own oxygenators. Then occurred the following milestones:

1966-1973
Cultural Revolution setback.

1972
Open-heart operations under acupuncture anesthesia.

1977
The Chinese developed a tissue bovine valve (and pericardial valves), which they still use.

1978
Counterpulsation was developed in China.

The hospital buildings seemed to be very old but clean and well organized. Equipment was scarce and to a large extent outmoded. Physicians' and nurses' gowns and bed sheets were clean, but sterile technique was not strictly observed—one could go into operating rooms with street clothes after donning cap, mask, gown and shoe covers.

Both Rui-Jin and Third People's hospitals were doing 20 open-heart operations per month. Most of these (70%) were operations for rheumatic valve disease. The rest were for congenital or vascular disorders. Third People's Hospital seemed to be better equipped for doing open-heart procedures than did Rui-Jin. Most children had their open-heart operations at Xin-Hua Hospital.

Rui-Jin Hospital has 1,200 beds and six operating rooms. The catheterization laboratory is only adequate for studies of the right side of the heart. The echocardiographic machine was out of order during our visits. Only two to three open-heart operations are done weekly, yet a hyperbaric operating room chamber is available, now used mostly for degenerative retinal diseases and a variety of medical conditions. The modestly equipped surgical intensive care unit (SICU) has three beds.

Third People's Hospital has 650 beds and handles as many as 3,500 to 4,000 outpatients a day. The cardiovascular surgical department has 50 beds and manages four open-heart operations per week. The three to four beds in the SICU are modestly equipped. The catheterization laboratory at this hospital is better equipped, with Japanese-made monitors and an x-ray machine, but still lacks cineangiography.

Zing-Hua Hospital is a large hospital that has 820 beds and handles 5,000 outpatients a day. Of its 1,100 staff, there are about 200 physicians and 600 nurses. Students from the Second Medical College make their clinical pediatric rotation at this hospital, which manages three to four congenital open-heart operation cases a week. There are 25 cardiovascular surgical beds and a 4-bed SICU.

All Chinese physicians and nurses have permanent government jobs, but with the low salaries of $100 to $150 per month they lack incentive. Many of the physicians speak some English, none very well. Many are well read, and most have a good idea about recent developments in heart surgery.

The second day (November 2) was spent opening cartons, distributing equipment and choosing patients for a surgical procedure. We took about two tons of equipment. Most of the "hardware" machines were loaned by the respective companies (cardiac monitors, respirators, recorders and the like). A vast amount of disposable equipment was taken to China and left there at the end of the trip. Operations done are outlined in Table 1.

Our cardiologists worked almost every day (mainly in the catheterization laboratory of Third People's Hospital). They relied on videotape angiography because no cine equipment was available.

General Notes on Chinese Medical Personnel in Both Hospitals

At Third People's Hospital, personnel were better motivated and generally more geared to taking care of cardiac patients than those at the other two hospitals.

Chinese physicians, nurses and technologists were courteous and willing to work hard and for long hours. They asked questions politely and rarely ventured to express their opinions. When they did, their comments were generally pertinent. Occasionally, their questions displayed a lack of knowledge of today's medicine. Just as occasionally, their comments indicated surprisingly advanced knowledge. All were eager to help and to take care of patients. Nurses and laboratory reports were generally reliable. Our tour guide commented, "You American doctors work very hard to take care of patients—just like Chinese doctors."

Conferences and discussions were given extra weight—

TABLE 1.—*Schedule of Open-Heart Operations Carried Out in November 1982 in People's Republic of China*

Oate	*Operation*	*Hospital*
Nov 3.	Aortic valve replacement	Rui-Jin
Nov 8.	Mitral valve replacement	Third People's
Nov 9.	Aortocoronary bypass	Third People's
Nov 10.	Mitral valve replacement	Rui-Jin
Nov 11.	Aortocoronary bypass	Rui-Jin

every case needed to be discussed at the "tea table" before the operation. Every day started with a joint conference of the two teams. Emphasis was also placed on eating every few hours, yet none of us gained weight, possibly because Chinese food is generally low in calories.

Video films were taken of two of the operations and physicians and nurses frequently took notes. The Chinese wanted to learn everything we had to offer. The Chinese heart-lung machine and bubble oxygenator are rough copies of our Sarns and Bentley.

Postoperative care was generally poor, mainly due to poor facilities. Moving patients from the operation room to the intensive care unit was a chore. The first and last cases turned out to have many postoperative problems that could have been avoided had the operations been done in the United States.

Surgeons seemed to be good with their hands but lacked basic skills in postoperative care. Nurses seemed to be hard-working and conscientious. Hardly any nurse spoke English.

General Notes on Facilities in Both Hospitals

Operating rooms. The operating rooms were very modest in general. Lights were poor and equipment was obsolete. Sterile technique was not strictly observed, although everything seemed clean and the rate of postoperative infections, we were told, was low. We had some trouble using the Chinese pump and connections.

Intensive Care Unit. A thoracic surgeon was in charge of the intensive care unit (ICU), which is rarely visited by cardiologists. At Rui-Jin, the ICU was technically fit to take care of one patient although it was originally designed for four. Local monitors did not work half the time. No facilities were available for modern IV lines. Respirators were rarely, if ever, used. Fresh-frozen plasma or platelet transfusions were not available. At Rui-Jin, the portable x-ray machine was about 50 years old. Because of poor ICU care, patients were left in the operating rooms for three to four hours after a heart procedure until they could be extubated before transfer to ICU. In the United States, patients are intubated in the ICU for about 24 hours.

Catheterization laboratories. Catheterization laboratories were deficient. Cine films were not used. Adequate resuscitation equipment was not available. These laboratories are run by radiologists.

General Comments on Chinese Patients

Chinese patients are very stoic. They do not complain much, but they do very little to help themselves and fail to adequately follow postoperative treatment instructions. We have not noticed the display of emotion by family members as is so common in other Third World countries.

Other Activities

During the first two weeks, we had time for the following sightseeing: a Shanghai boat ride, Westlake and Hang Zhou resort cities near Shanghai, a Buddhist temple, a pagoda, Westlake park and gardens, a goldfish lake, a silk factory, the Shanghai zoo, a bamboo factory, the Shanghai ballet *(Swan Lake)* and Dragon Springs. We also had a group picnic.

Scientific lectures included topics like coronary bypass operation accompanied by a movie film, the diagnosis and clinical manifestations of coronary artery disease and postoperative care. During a reception given by the President of Second Medical College, plans were made for further cooperation and an exchange program between St Mary's Hospital and Shanghai Second Medical College.

On the last day (November 13) we visited the following places: Palace of Heaven, Forbidden City, National Museum, Mao's Mausoleum, the Great Wall of China, the Summer Palace of the Ming Dynasty and the Burial Place of the Jing Dynasty.

The 1983 Visit

This second visit served to enforce both the spirit of friendship between American and Chinese team members and the expertise gained by the Chinese personnel during the first visit. It was clear to all of us that heart surgery in China had improved remarkably over one year. We were excited and satisfied by the thought that we had contributed positively to this progress. Our team performed several operations during this visit and the atmosphere was that of a routine working schedule. The Chinese had in the meantime acquired or replaced much essential equipment that was lacking or not operational just a year before. We were amazed to see how their industrial institutions had successfully copied many of our basic products including machines, supplies and supportive medical systems. But more significant was the air of confidence and improved technical skills that characterized our Chinese co-workers. Improved also was their use of the English language. Most of the negatives of the 1982 trip were eliminated or greatly alleviated in 1983. This certainly attests to the great potential the Chinese people have and to their determination to catch up with advanced western medicine and technology. Their glorious history leaves little doubt that they will be successful in their drive. A seven-member team from China visited us in San Francisco in May 1984 for six weeks, during which time they gained more experience in our open-heart methods and more knowledge and an understanding of our way of life. More trips by our team to China are planned.

Commentary

Some Facets of Alternative Medicine—Today and Yesterday

MICHAEL C. LIVINGSTON, MD, *Richmond, British Columbia*

With medical costs still rising relative to gross national product, certain observers have wondered whether such costs could be reduced by decreasing the number of practicing physicians.[1] Meanwhile, relatively less is known about the use of alternative health practitioners.[2]

On one day in February 1984 I examined three patients whose cases may shed some light on the problem of alternative practitioners. I see similar cases fairly frequently for I am a family physician who also sees referred patients with neck or back problems.

Brief Reports of Cases

Case 1

The patient, a 20-year-old North American-Chinese woman* who was currently unemployed, had been an exercise teacher at the YMCA.

In June 1983 she had had a sudden pain in her lower back, but had danced for an hour before stopping. She received medication from her family doctor and was advised to rest, being reassured that the pain would go away. When it continued, she was referred to a rheumatologist who diagnosed a "short right leg syndrome" and recommended raising the heel. The pain became worse. She consulted a physiotherapist at a sports medicine clinic, was given 16 electrical treatments but no education and with no improvement. She then turned to the alternative healers, making about 40 visits to three separate chiropractors over the next few months. The chiropractors said rather different things, but from one she had full-body x-ray studies that "revealed" the following: a high right pelvis, a low right shoulder, a high right ear, a displaced second cervical vertebra, another displaced vertebra at about T-10, a sacrum twisted to the left, and her left pelvis twisted to the front—oh yes, and a short right leg.

There were many differences among the various therapists concerning causes and management.

She was currently attending a chiropractor who "just touches your neck." He makes a "specially delicate adjustment." The adjustment was so delicate in fact that the patient would not let me examine her neck because I might disturb it.

Not being able to examine her, I spent additional time in educating, explaining the various factors that contribute to pain—injury, tension, posture, past and family experience, treatment and so forth. I tried to open her understanding, to show her that she was being programmed into "becoming a patient," just as Pavlov's dogs had been programmed to salivate. I offered to teach her an effective posture and a relaxation and exercise program she could do at home, if she wished to return for a second visit.[3]

Case 2

The next patient, a 56-year-old real estate agent,* four months previously had suffered her fourth (rather minor) motor vehicle accident and was apparently having severe low- and mid-back pain.

She had consulted her family physician, who had agreed with her going to a chiropractor. After three months her physician suggested a physiotherapist who seemed more helpful to the patient, but he went on holiday and his replacement made her feel worse. She also saw a podiatrist who said her feet were in terrible shape and her back would never be right until her feet were right. The patient then began seeing a reflexologist.

In effect, her condition was unchanged over 4½ months.

On examination there were minimal findings except for pain on hyperextension of the lumbar spine. She seemed basically to be suffering from tension, anxiety and depression—she cried a lot during her visit—and from a lack of understanding of the natural course of her injury and from overtreatment. The natural history of her problem was explained and she was shown basic flexion pelvic tilting exercises with instructions to increase these gradually over a month and to walk daily. I suggested that she attend fewer therapists.

Case 3

The third patient, a young guitarist, had had low back pain for two weeks, accentuated by sitting and forward and back bending. He had trigger points to the right of L-5 and in the right gluteus medius. His straight-leg raising was limited to

*This patient was referred by Peter Chang, MD, of Richmond, BC.

*This patient was referred by Don Stewart, MD, Vancouver, BC.

(Livingston MC: Some facets of alternative medicine—Today and yesterday [Commentary]. West J Med 1985 Aug; 143:269-270)

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60 degrees on the right side. There were no neurologic abnormalities.

While I was discussing with him the natural history of his problem, showing him three basic back exercises and using one manipulation on the right side at the fifth lumbar level, he told me of his past experience.

Three years previously he had had a two-year episode of lower back pain. He spent 20 visits receiving ultrasound from a physiotherapist and then some 70 visits being adjusted by a chiropractor, who he thought was good. The chiropractor gave him little education and the patient had a very limited exercise program. The physiotherapist apparently had not attempted any education.

While on a musical tour, his back still somewhat sore, he was walking with his wife down a side street in Regina, Saskatchewan, when a large jackrabbit jumped up on the edge and bounded away along the sidewalk. "Something came back to me from my childhood and I started to chase after the jackrabbit. The rabbit turned sharply right, I tried to turn also, and slipped on the ground, landing on my back. I got up and the pain had gone."

The jackrabbit adjustment had succeeded where 20 physiotherapy visits and 70 chiropractic adjustments had failed.

Discussion

These cases suggest a certain difficulty in exact diagnosis and a confusion of treatment and overtreatment both from alternative healers—in this instance, chiropractors—and possibly from physiotherapists. The actual cost of such care may be considerable. While these anecdotal cases are few, such description remains valid.[4] Further, I have over the past 18 years, while examining more than 6,000 patients with back and neck problems, encountered numerous similar cases. "People" have been turned into "patients" whom a therapist then "heals." Too frequently, dependence has been nurtured and self-care not encouraged.

Some of the strengths and weaknesses of alternative medicine were discussed by the surgeon Sir James Paget in a classical lecture in 1867, "Cases That Bone-Setters Cure."[5]

He noted that manipulating joints sometimes helped.

> Cases of this kind are of frequent occurrence. To the bone-setter, every injured joint is "put out"; and the one method of cure is the wrench and the rough movements, by which it is said that the joint is "put in" again.
>
> Now, it would be of little use to us to estimate, even if it were possible, the quantity of mischief done by treatment such as this. It is more important to know and consider that it sometimes does good; that, by the practice of it, bone-setters live and are held in repute by the ignorant of all classes everywhere.

He observed further that, "The patients who are cured never cease to boast of their wisdom in acting contrary to authorized advice; but they who are damaged are ashamed of themselves, and hold their tongues." Paget well described the magical effect of the alternative healer:

> If nothing in it but its portion of the nervous system is in fault, this may be sometimes cured through influence on the mind. And so not only bone-setters, but the workers with Mesmerism, and tractors, and oils, and distant or superficial electricity, can sometimes cure hysterical joints: for the patients love to be cured with a wonder; and the audacious confidence of all these conjurors is truly wonderful.

Finally, he adjured physicians to "learn then to imitate what is good and avoid what is bad in the practice of bone-setters," advice that the medical profession largely ignored.

More than 100 years have passed and Paget's principles still hold good for the alternative healers of today. Chiropractors have replaced bone-setters. Other alternative healers flourish for the very reasons that Paget described. Four other reasons may attract patients to these healers.

First, there is today general confusion and suspicion about science and some of its frightening effects. The environment is being threatened, some foods contain additives, drugs are responsible for side effects as well as benefits and the nuclear threat looms above all.

Alternative healers offer simple solutions without the bother of making an exact diagnosis. They may emphasize health rather than the absence of disease.

Second, most diseases are self-limiting or chronic. All healers receive some undeserved credit for healing when actually they are overseeing the natural course of an illness.

Third, modern diagnosis may involve the use of expensive technology and admissions to hospital. Physicians may not be much increasing their own fees, but they do generate higher costs by their use of modern technology,[6] multiple referral and hospital care. Alternative healers treat primarily an ambulant population and rarely make an exact diagnosis, so they rarely require such aids. The general public is often unaware of the lack of standards among such healers.

Finally, alternative healers usually have limited treatment options. Therefore, they concentrate on the most important treatment option of all, the healer-patient relationship. They concentrate on listening, on direct touch and on convincing patients. Direct contact used to be foremost in classical medicine.

Today science may stand in the way of our personal communication with our patients, as Norman Cousins recently noted:[7]

> Every time you go to a referral or to a diagnostic machine and then a referral beyond the diagnostic machine, you are increasing the distance between yourself and the doctor who is such a powerful ingredient in helping set you right.

Could alternative healers despite their weaknesses be, in effect, showing the medical profession the path to more effective healing—direct communication with patients?

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Demographics and Disease Prevalence of Two New Refugee Groups in San Francisco

The Ethiopian and Afghan Refugees

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Of all the Ethiopian (N = 110) and Afghan (N = 59) refugees seen at the Refugee Screening Clinic at San Francisco General Hospital Medical Center between May 1982 and July 1983, most were young men and more than 80% of each group were unable to speak English. The most frequently noted medical conditions in both groups were pathogenic parasites, dental caries and skin disorders. Most had positive PPD tests, but only a few cases of class A or class B tuberculosis were found. Among the Ethiopians two active cases each of Plasmodium vivax *malaria and trachoma were diagnosed. Although a wide range of diseases were seen, most were common rather than exotic. In addition to the need for translators, traditional beliefs and customs must be sensitively considered when providing health care to these groups.*

(McCaw BR, DeLay P: Demographics and disease prevalence of two new refugee groups in San Francisco—The Ethiopian and Afghan refugees [Cross-cultural Medicine]. West J Med 1985 Aug; 143:271-275)

During the past ten years, nearly 1 million refugees have been admitted to the United States.[1] Most have come from Indochina, but since 1980 significant numbers of refugees from other troubled areas of the world have also resettled here. In this report we describe the demographic characteristics and health problems of two refugee groups new to the United States, the Ethiopians and the Afghans. Although the two groups differ in fundamental ways, they share the common experiences of being displaced from their homes, a lack of familiarity with Western culture and having many similar health problems.

Afghans represent the largest group of refugees in the world today.[1,2] As of June 1983, about 12,000 Afghans have come to the United States as refugees.[3] Ethiopians form the third largest group of refugees in the world.[1] As of October 1983, about 10,000 Ethiopians officially classified as refugees have been admitted to the United States.[3] In addition, an estimated 10,000 to 40,000 Ethiopians who are not officially classified as refugees are currently living in the United States. Both of these refugee groups have been resettled throughout the country but the largest percentage have settled in California. If the admissions ceiling for these groups remains constant, between 3,000 and 6,000 Afghan refugees and 2,500 to 3,000 Ethiopian refugees are expected to relocate in the United States each year.[4]

Ethiopian and Afghan refugees are allocated to various US areas based on previous family ties and current local refugee population densities. In San Francisco, the resettlement agencies set up initial appointments for the refugees at the Refugee Screening Clinic at San Francisco General Hospital Medical Center. More than 90% of the primary migrants receive evaluation at the clinic, which provides a central location for medical care. Interpreter services are available for all refugees during the initial medical screening and about four months of ongoing care.

The medical records of all Ethiopian (N = 110) and Afghan refugees (N = 59) who were seen at the Screening Clinic between May 1982 and July 1983 were reviewed. Demographic data and health information were obtained for all refugees. The health information included pertinent findings from the medical history and physical examination, a clinician's assessment of a refugee's medical condition and the results of laboratory tests (complete blood count, VDRL and examination of a stool specimen for ova and parasites). Puri-

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ABBREVIATIONS USED IN TEXT
HBsAg = hepatitis B surface antigen
PPD = purified protein derivative

fied protein derivative (PPD) testing was routine for all refugees younger than 21 years. Those older than 21 either received a PPD or a recent chest x-ray film was reviewed. The number of medical problems per patient and referrals to other clinics and specialties were determined. Obstetric information was also obtained for women of childbearing age (16 to 45 years old).

For the Ethiopian data, significance was tested by doing a χ^2 and a Fisher's exact test and the level of significance was set at $P = .05$. Only frequencies and raw data are reported for Afghans due to their small number. Although the findings presented here are based on a small, nonrandom sample—the first 110 Ethiopians and 59 Afghans screened—it is hoped that this study may serve as a guide to the health problems that may be seen elsewhere in such refugee groups and that it will stimulate studies in other localities.

The Ethiopian Refugees in San Francisco

"War, drought, civil strife and oppression have driven more than 1 million people out of Ethiopia during the past six years."[1] Conditions in Ethiopia are severe; at birth, life expectancy for men is 37 years, for women, 40.1 years, and infant mortality is 155 per 1,000 (D. Rosenthal, "New Ethiopia Emerges From Feudal Shadow of King Solomon," *San Francisco Chronicle,* Aug 7, 1983, p A15). Most Ethiopian refugees are poor and uneducated and have fled to the neighboring countries of Somalia, Sudan and Djibouti (G. Klein, "Ethiopian Refugees' Rough Road to US," *Christian Science Monitor,* Dec 30, 1982, p 7, and D. Winder, "Surge of Ethiopian Refugees Threatens Horn of Africa," *Christian Science Monitor,* April 26, 1983, p 1).[5-7] Until recently, however, most of those who have entered the United States have been from the educated classes, having left Ethiopia primarily because of political persecution or civil war.[8] Most are adept at urban living and familiar with Western ways and medical care. Nonetheless, they face considerable problems of adjustment once they have arrived here. Recently, rural Ethiopians have also begun entering this country. They tend to have medical conditions that reflect a more impoverished background and they are less familiar with Western culture and medicine.[9]

Demographics

Of this group of Ethiopians, 76 (69%) are male and 34 (31%) are female. The mean age is 22.7 years and the range is from 6 months to 50 years old.

Marital status. In all, 14 (13%) of the refugees are children (0 to 16 years old) and, among the adults, 74 (77%) are single and 22 (23%) are married. Of Ethiopian women older than 16 years, 39% are married. In contrast, only 17% of Ethiopian men are married.

About 30% came to the US with their immediate families, ranging in size from three to seven members.

Of the 28 women of childbearing age (16 to 43 years of age), 22/28 (79%) had no children, 3/28 (11%) had one or two children and 11% had four or five. At the time of screening, four (14%) of the women were pregnant.

Country of first asylum. The earliest Ethiopian refugees who arrived in San Francisco had been living independently in countries of first asylum. Initially, many arrived from Italy. More recently, refugees have come from camps located in Sudan and Djibouti. The average time spent in a refugee camp or other country before entering the United States was 21 months and the range was from 3 to 82 months.

Language. In the context of the screening clinic, the ability to speak English was defined as the ability to communicate effectively with a clinician about health problems or concerns. By this criterion, 84% could not speak English. The most commonly spoken languages were Amharic, the national language (80%), Tigregna (66%), Arabic (42%), Italian (13%) and Somali (7%). Two or more languages were spoken by 60% of the refugees.

Health Problems

General. The average number of medical conditions per person was 3.3. The standard deviation was 1.46 and the range was from 0 to 8. This determination was made for each refugee by adding the number of positive results on laboratory tests, the number of medical problems noted by a clinician and various health conditions. There were no significant differences in the number of medical problems between sexes or among age groups. Table 1 shows the most frequent medical conditions. A discussion of selected medical problems follows.

Tuberculosis. The determination of tuberculosis status was based on PPD results and chest film readings when pertinent. Before January 1983, PPD testing was not routinely done on patients older than 21 years unless it was clinically indicated. Since that time, PPD testing has been done on all patients, and those with a positive result (greater than 10 mm at 48 hours) receive a follow-up chest x-ray film.

Of those for whom adequate information was available (N = 44), 30% had negative PPD tests; 57% had positive PPD

TABLE 1.—*Most Frequently Reported Medical Conditions of the Ethiopian Refugees (N = 110) Based on Physical Examination*

Condition	Number of Cases	% of Those Tested
Stool specimen positive for pathogenic parasites (N = 89)	34	38
Dental caries	37	33
Dermatologic diseases (mainly tinea)	34	31
Gastrointestinal complaints (including constipation, abdominal cramping, peptic ulcer disease)	28	25
Musculoskeletal complaints	23	21
Gynecologic problems (mainly dysmenorrhea)	9	32 (N = 28)
Pregnancy	4	14 (N = 28)
Refractive errors	14	13
Thyromegaly	14	13
Headaches	13	12
Ear disease	13	12
Trachoma, or history of trachoma	10	9
Respiratory tract complaints	10	9
Positive VDRL	8	7
Physiologic cardiac murmur	8	8
Tuberculosis, class A or B	6	5
Trauma	5	4

tests and a normal chest film; 11% had positive PPD tests, an abnormal chest film but no evidence of active disease (class B), and 2% had positive PPD tests, an abnormal chest film and evidence of active disease (class A).

Other conditions. Two cases of active malaria *(Plasmodium vivax)* were diagnosed. A history of malaria was reported by 36% of this group of Ethiopians. Thyromegaly was present in 14 (13%); 12 of the 14 cases were female. Essentially all of these cases were of iodine-deficient endemic goiter. Ten (9%) persons showed evidence of active trachoma or recent infection by *Chlamydia.* Both a slit-lamp examination of the cornea and tarsal plates and identification of inclusion bodies in scrapings of the conjunctiva are necessary to distinguish active from inactive trachoma.

One case each of shigellosis and gonorrhea was diagnosed. No cases of filariasis, onchocerciasis, leishmaniasis, schistosomiasis, cholera, yellow fever, typhoid, typhus, relapsing fever or Hansen's disease were identified. These conditions are all known to exist in Ethiopia and the surrounding countries.[9-11]

There were 28 women of childbearing age in this group. As noted previously, 4 (14%) of the women were pregnant at the time of screening. Of the 28 women, 3 (11%) indicated that they were using some form of birth control. When asked, 19 (70%) stated that they wanted gynecologic services, which included pelvic examinations, Papanicolaou smears, birth control counseling and evaluation of pelvic pathologic conditions.

Laboratory Findings

Stool specimen examinations. Stool specimens were submitted for ova and parasite testing by 81% of the Ethiopians. Pathogenic parasites were found in 38% of those tested. There were no differences between male and female refugees in frequency of positive stool results. However, there were significant differences ($P = .004$) between age groups: Ethiopians aged 0 to 10 years and 30 to 40 years had the highest frequency of positive results. The parasites identified are listed in Table 2. Due to cost constraints, generally only one stool specimen per refugee was examined. Pathogenic parasites would likely be found in a greater percentage of Ethiopians if two or more stool specimens were examined. Most of the patients were asymptomatic and were treated according to the protocols stated in *The Medical Letter* (January 22, 1982). The two cases of *Schistosoma mansoni* showed no evidence of hepatic injury, colitis or polyposis.

Serology. VDRL reactivity was tested in all Ethiopians older than the age of 12 years and 8% were reactive. There were no associated symptoms, thus these cases were classified as latent syphilis and treated according to standard protocol. There was no difference between male and female refugees in the frequency of positive VDRL results. Due to cost, this population was not routinely screened for hepatitis B surface antigen (HBsAg) and no one was found to have active hepatitis. A recent study has found the prevalence of the HBsAg carrier state among Ethiopians to be 8%.[12] Thus, screening of pregnant women and administering the combined hepatitis B immunoglobulin and hepatitis B vaccine to neonates would be advised.

TABLE 2.—*Pathogenic Parasites Found in Ethiopian Refugees*

Parasite	Number of Cases	% of Those Tested
Giardia lamblia	15	16
Hymenolepsis nana	9	10
Entamoeba histolytica	6	7
Strongyloides stercoralis	5	6
Hookworm species	4	4
Schistosoma mansoni	2*	2
Trichuris trichiura	1	1

*In addition, 1 patient had a history of disease.

TABLE 3.—*Most Common Referrals of Ethiopian Refugees to Specialty Clinics**

Service	Number of Patients	% of All Ethiopians
Ophthalmology	26	23
Dental	18	16
Gynecology	15	†
Family Planning	2	†
Tuberculosis	10	9
Orthopedics	8	7
Ear, Nose and Throat	7	6
Cardiology	6	5

*Less frequent referrals included endocrinology, neurology and gastroenterology
†Considering Gynecology and Family Planning specialties together, 60% of women aged 16 to 45 years were deferred.

Referrals

The majority (67%) of the Ethiopians received at least one referral to specialty clinics. The most common referrals are presented in Table 3.

Cultural Considerations

The strong cultural pride of the Ethiopians plus their traditions of courtesy and reserve may prevent them from asking questions when they do not understand what is being communicated. While many refugees can speak some English, their ability to discuss their health problems and to comprehend our medical explanations may be limited. Therefore, the need for translators is critical. Since many fled Ethiopia because of political repression, they may be fearful that what they disclose could jeopardize family or friends who remain at home. Thus, the assurance of confidentiality and a sensitivity to their beliefs and customs is vital when providing services to this population. Health providers should also be aware of the possible history of torture when evaluating the physical and mental health of this group. Several refugees showed physical evidence of torture, mainly scars as a result of second- and third-degree burns.

In general, Ethiopians are comfortable and familiar with the use of Western medicine for some diseases, such as antibiotics for venereal disease. Nevertheless, they often maintain their own traditional beliefs and habits in regard to other health problems, such as herbal remedies for parasites and scarification around the eyes as a treatment for trachoma.[13] The controversial practice of clitorectomies on young girls is still being done in Ethiopia and some of the surrounding countries. Likewise, removing the uvula from young children is a very common practice and was frequently seen in the Refugee Clinic. Uvulectomy is generally done by a village healer, presumably to prevent recurrent throat infections.[9]

The Afghan Refugees in San Francisco

In 1978, after a political coup, a large number of Afghans fled from their country. The subsequent invasion by the Soviet Union in December 1979 caused further refugee movement.[14] There are now more than 3 million Afghan refugees living outside Afghanistan—many in camps in Pakistan and others seeking shelter in Iran, Turkey, India and various countries of Europe.[7,15]

Usually, the first wave of refugees to arrive in the United States from a particular country is from the better educated, upper classes. This reflects both the US immigration policies and the greater ease with which these people can leave their own country.[16] In general, this trend seems applicable to the Afghan refugees screened at the San Francisco General Hospital Refugee Clinic.

Demographics

Of this group of Afghans, 38 (64%) are male and 21 (36%) are female. The mean age is 24 years old, ranging from 6 months to 62 years. Children between the ages of 0 and 10 years make up about 30% (17) of this group and 51% of the adults are between the ages of 20 and 40.

Marital status. More than two thirds of the Afghan refugees came to the US with members of their immediate family. Family sizes vary from two to seven, and the mean family size is four members. About half of the adults are married. Of the Afghan women older than 16 years, 83% are married. In contrast, 36% of Afghan men older than 16 are married.

There were 13 women of childbearing age, and 10 had children. The average number was 2.8, but the range was from 1 to 10 children. Of the 13 women, 5 said that they were using some method of birth control. No current pregnancies were diagnosed at the time of screening.

Language. Within this group of Afghans, 47 (80%) could not speak English. The most commonly spoken languages were Dari (34 [58%]), which is a dialect of Persian, and Pashto (24 [41%]), a language also spoken by Pakistanis in the southeastern part of the country.

Health Problems

General. The average number of medical conditions per person was 2.2. No medical problems were found in five persons (9%); four or five problems were found in nine (15%). The most frequent medical conditions reported by the clinicians are listed in Table 4.

TABLE 4.—*Most Frequently Reported Medical Conditions in the Afghan Refugees Based on Physical Examination (N = 59)*

Condition	Number of Cases	% of Those Tested or Examined
Dental caries	24	41
Dermatologic disorders (tinea, scabies, eczema)	22	39
Stool specimen positive for pathogenic parasites	16	36
Gastrointestinal disorders (including constipation, peptic ulcer disease)	14	23
Musculoskeletal complaints, pain	7	12
Refractive errors	6	12
Hypertension	5	9
Hearing deficits and/or speech disability	3	5
Headaches	3	5
Physiologic cardiac murmurs	3	5

No Afghans had active malaria or a history of malaria. No cases of dracunculiasis, filariasis, leishmaniasis, shigellosis, cholera, typhoid, typhus, Hansen's disease or trachoma were identified. All of these diseases are known to exist in Afghanistan.[17]

Tuberculosis. The tuberculosis status of this group of Afghans is as follows: 10 (17%) had negative PPD tests, 32 (54%) had a positive PPD test and a normal chest film and 3 (5%) had a positive PPD test and an abnormal chest x-ray film but there was no evidence of active disease (class B).

There were no cases of active (class A) tuberculosis. In 13 (22%), the tuberculosis status could not be determined from the medical record because of inadequate information.

A breakdown of tuberculosis status by age shows that 59% of those refugees younger than 20 years had positive PPD results, whereas in those older than 20 years, 97% had positive PPD results.

Stool specimen examinations. Of this group of Afghans, 51 (86%) were tested for ova and parasites. Pathogenic parasites were identified in 18. Two age groups had the highest frequency of positive stool specimens: those between 0 and 10 years, and those between 20 and 30 years old. The parasites that were identified are listed in Table 5. Hookworm species and *Strongyloides stercoralis,* which are endemic in Afghanistan, were not identified in this population.

Serology. VDRL reactivity was tested in those older than 12 years, who represented 69% of the Afghans. None were reactive. This population was not routinely screened for hepatitis B surface antigen.

Anemia. Values for hemoglobin, hematocrit and mean corpuscular volume were available for all but three Afghans. The most common abnormality, a low mean corpuscular volume or microcytosis, was noted in nine (15%) Afghans. This condition usually results from iron deficiency, thalassemia or a hemoglobinopathy. Further diagnostic tests were not done.

Referrals

Of this group of Afghans, 30 (51%) received at least one referral to specialty clinics. The most common referrals were made to dental, seven (12%); family planning or gynecology or both, seven (12%); ophthalmology, six (10%), and tuberculosis clinics, six (10%).

Cultural Considerations

As a Near East Muslim country, Afghanistan has a strong religious tradition. This heritage is important to most refugees. Other cultural values include the importance of the extended family; respect for the advice and decisions of elders; traditional male and female roles, and a sense of privacy and modesty, especially among the women. A sensitivity to these

TABLE 5.—*Pathogenic Parasites Found in the Afghan Refugees Screened*

Parasites	Number of Patients	% of All Tested (N = 51)
Ascaris lumbricoides	5	9
Giardia lamblia	5	9
Entamoeba histolytica	4	7
Hymenolepsis nana	3	5
Trichuris trichiura	1	2

beliefs and customs will greatly increase the effectiveness of those who provide services for the Afghans.[17,18]

Discussion

The majority of both the Ethiopian and Afghan refugees seen in San Francisco are young men. Whereas most of the Ethiopians are single adults, most Afghans have come to the United States with their families. More than 80% of each group cannot speak English, and the need for translators, especially in a medical setting, is critical.

Pathogenic parasites, dental caries and dermatologic disorders were the most frequently noted medical conditions in both groups. Most Afghans and Ethiopians had positive PPD tests, but there were few cases of class A or B tuberculosis. A third of the Ethiopians have a history of malaria although there were only two active cases. Similarly, 7% had a history of trachoma, but there were only two active cases. However, examination of the everted tarsal plate should be included in the routine examination of this population. No cases of malaria or trachoma were found among the Afghans. Gastrointestinal and musculoskeletal disorders were frequent in both groups; pregnancy and thyroid disease, particularly endemic goiter, were noted more frequently among the Ethiopians.

As is true with other recently arrived refugee groups, the Ethiopians and Afghans are often depressed and agitated as a result of being away from their country and culture and having experienced the loss of family and friends.[19] While the outward signs may be subtle or confusing, health care practitioners should take this into account when diagnosing and providing care for these populations.

Although a wide range of medical problems is seen in these two refugee groups, the problems are common rather than exotic and do not pose a public health hazard. The Ethiopians and the Afghans, with their unique histories and cultures, have much to contribute to the United States. A sensitive understanding of their particular health care needs and problems will ease their entry into our society.

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Allergy Practice in California

Diagnostic and Therapeutic Methods Used by Allergists and Otolaryngologists

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In 1982 the Scientific Board of the California Medical Association (CMA) established an interspecialty subcommittee to assist the Scientific Advisory Panel on Allergy and the Scientific Advisory Panel on Otolaryngology/Head and Neck Surgery in responding to medical practice questions on a variety of controversial methods of diagnosis and treatment of allergic conditions. The subcommittee of three allergists and three otolaryngologists, board certified in their respective specialties, was charged with identifying the common ground and defining the differences between the two specialties on such questions as cytotoxic testing for food allergy, sublingual testing and treatment for food allergy, endpoint titration for the diagnosis of inhalant allergy, the radioallergosorbent test (RAST), provocative-neutralization techniques for food allergy and autogenous urine injections for allergy therapy. The subcommittee's work was an extension of an informal dialogue begun by the advisory panels in 1979. The opinions subsequently recommended by the subcommittee on these questions were reviewed and endorsed by the parent advisory panels and received final approval from the CMA Commission on Quality Care Review.

To prepare for its in-depth evaluation of the issues cited, the subcommittee felt it essential to determine the frequency with which some of the more controversial techniques were used. It was apparent at the outset, however, that no such information about the actual use of diagnostic and therapeutic methods by practicing physicians existed; the subcommittee therefore surveyed CMA members for this purpose.

Methods

A questionnaire was prepared requesting specific information about the frequency of the use of various methods, both established and controversial, in the diagnosis of allergic disease and in allergen immunotherapy. It was mailed in February 1983 to all members of the California Medical Association who designated their specialty as either allergy or otolaryngology/head and neck surgery. This survey included questions about training, board certification and practice characteristics.

Questions about each test and treatment procedure were designed to elicit an estimate of the percent of new patient allergy evaluations in which the test or treatment was used.

Results

Questionnaires were sent to 201 allergists and 586 otolaryngologists; replies were received from 103 (51%) and 186 (32%), respectively. In all, 79 otolaryngologists indicated that they do not treat allergic disease, so the results were based on the remaining 107 (18%) otolaryngologists.

Allergy Training and Board Certification

Residency, fellowship, preceptorship training and board certification of respondents are shown in Table 1. Of the allergists, 83.5% had one or more years of residency in either internal medicine or pediatrics and 71.8% had postresidency allergy fellowship training. Of the otolaryngologists, 94.4% had one or more years of residency in that specialty and 4.7% reported allergy fellowship training.

Regarding board certification, 75.7% of the allergists responding were certified by the American Board of Allergy and Immunology, a conjoint board of the American Board of Internal Medicine and the American Board of Pediatrics. Among the otolaryngologists, 97 (90.7%) were board certified in that specialty, but only one in allergy and immunology.

TABLE 1.—*Training and Board Certification of 103 Allergy and 107 Otolaryngology/Head and Neck Surgery (Oto/H&N) Respondents*

	Allergy Number (%)	Oto/H&N Number (%)
Residency and Fellowship		
Residency (1 or more years)		
Family Practice	4 (3.9)	1 (0.9)
Pediatrics	38 (36.9)	1 (0.9)
Internal Medicine	48 (46.6)	2 (1.9)
Oto/H&N	6 (5.8)	101 (94.4)
Other	7 (6.8)	5 (4.7)
Allergy Fellowship	74 (71.8)	5 (4.7)
Preceptorship	11 (10.3)	20 (19.4)
Board Certification		
American Board of		
Family Practice	2 (1.9)	0 (0.0)
Internal Medicine	22 (21.4)	0 (0.0)
Pediatrics	26 (25.2)	0 (0.0)
Oto/H&N	4 (3.9)	97 (90.7)
Allergy and Immunology	78 (75.7)	1 (0.9)
Other	0 (0.0)	2 (1.9)

(Terr AI, Weisskopf A, Sparacino RA: Allergy practice in California—Diagnostic and therapeutic methods used by allergists and otolaryngologists [Information]. West J Med 1985 Aug; 143:276-279)

A report of the Interspecialty Subcommittee of the Scientific Advisory Panels on Allergy and Otolaryngology/Head and Neck Surgery of the Scientific Board of the California Medical Association. Drs Abba I. Terr and John A. Metheny were co-chairs of the subcommittee; the other members were Roger M. Katz, MD; W. Hugh Powers, MD; Alex Weisskopf, MD, and Ned J. Whitcomb, MD. Mr Sparacino is manager of the Department of Specialty Sections and Scientific Programs, California Medical Association.

Reprint requests to Robert A. Sparacino, Department of Specialty Sections and Scientific Programs, California Medical Association, 44 Gough Street, San Francisco, CA 94103.

Practice Characteristics

On the average, the ratio of adults to children in allergy practice is 2:1 for allergists and 4:1 for otolaryngologists. There is a large variation within individual practices, and a few physicians restrict their allergy practice to a particular age group. For allergists, the mean number of new cases per week was 8.7 ± 5.4; for otolaryngologists it was 4.9 ± 5.1.

TABLE 2.—*Type of Disease Seen in Allergy Practice (% of New Allergy Patients)**†

	Allergy	Oto/H&N
Nasal	54.8 ± 18.5	82.5 ± 20.9
Asthma	31.2 ± 14.5	8.5 ± 12.0
Food allergy	8.4 ± 10.6	11.6 ± 14.9
Urticaria	6.1 ± 4.4	4.3 ± 5.9
Gastrointestinal	4.3 ± 8.3	3.5 ± 5.0
Chemical allergy	3.5 ± 7.2	3.1 ± 3.4
Other	4.6 ± 5.8	8.2 ± 13.6

Oto/H&N = otolaryngology/head and neck surgery

*Mean ± 1 standard deviation.

†Total percentage may be greater than 100% because some patients present with more than one disease.

Table 2 shows that nasal allergy is the most common type of disease seen by both groups, constituting approximately 55% of the cases seen by allergists and 83% by the otolaryngologists. Allergists see a considerably higher percentage of patients with asthma.

Diagnostic Tests

The immediate hypersensitivity skin test in which a cutaneous wheal and erythema appears 15 to 20 minutes after application of an allergen is well established in allergy diagnosis. Despite the long tradition of the test, different methods for applying the allergen are used in clinical practice. Table 3 shows the respondents' use of the prick (puncture), scratch, single-dose intracutaneous (intradermal) and serial endpoint titration methods for diagnosing inhalant and food allergy.

The RAST detects specific IgE antibodies in serum. Table 4 shows the usage of RAST in the diagnosis of allergy to inhalants, foods and other allergens such as venom, drugs or occupational allergens. Table 4 includes data on the use of total serum IgE in diagnosis.

Controversial methods are used by only a handful of the respondents, as shown in Table 5. The cytotoxic test is based

TABLE 3.—*Diagnostic Tests for Initial Workup—Skin Test Method**

Test	Specialty	Percentage of Patients 0%	1-5%	6-25%	26-50%	51-75%	76-100%
Prick test—inhalants	Allergy	23	6	2	5	14	50
	Oto/H&N	77	6	5	5	1	6
Prick test—foods	Allergy	33	16	17	10	5	19
	Oto/H&N	87	7	1	1	0	4
Scratch test—inhalants	Allergy	56	5	5	5	6	23
	Oto/H&N	73	5	7	3	4	8
Scratch test—foods	Allergy	63	7	8	6	7	9
	Oto/H&N	92	3	3	1	0	1
Intracutaneous—inhalants	Allergy	10	5	7	21	23	34
	Oto/H&N	68	12	7	1	7	5
Intracutaneous—foods	Allergy	52	14	9	6	5	14
	Oto/H&N	88	4	5	0	1	2
Endpoint titration—inhalants	Allergy	89	3	1	2	1	3
	Oto/H&N	41	13	7	3	5	31
Endpoint titration—foods	Allergy	92	4	0	0	3	0
	Oto/H&N	84	12	3	0	0	1

Oto/H&N = otolaryngology/head and neck surgery

*Figures are percent of respondents in each specialty reporting frequency of usage of each method identified in the first column. Total percentage may diverge from 100% because of rounding errors.

TABLE 4.—*Diagnostic Tests for Initial Workup—In Vitro Methods**

Test	Specialty	Percentage of Patients 0%	1-5%	6-25%	26-50%	51-75%	76-100%
RAST—inhalants	Allergy	52	40	5	1	1	1
	Oto/H&N	39	30	12	5	6	9
RAST—foods	Allergy	48	43	6	1	1	1
	Oto/H&N	54	23	12	2	4	5
RAST—other	Allergy	61	30	5	1	1	1
	Oto/H&N	76	15	5	0	2	2
Serum IgE	Allergy	18	46	16	5	6	8
	Oto/H&N	37	30	9	6	8	10

Oto/H&N = otolaryngology/head and neck surgery, RAST = radioallergosorbent test

*Figures are percent of respondents in each specialty reporting frequency of usage of each method identified in the first column. Total percentage may diverge from 100% because of rounding errors.

on changes in leukocyte morphology after in vitro exposure to food extracts. Provocation-neutralization techniques consist of exposing a patient to a test substance to observe the presence of subjective symptoms over a subsequent ten-minute period. The testing is done by either injecting a substance intracutaneously or subcutaneously, or by applying a drop sublingually. Measurement of wheal diameter following intracutaneous injection and the occurrence of objective physical findings are also noted at times, but subjective symptoms are the primary indications of a positive result.

Immunotherapy

Treatment of allergic disease usually requires a broad-based program of environmental precautions or restrictions, symptomatic medication and, in some cases, immunotherapy consisting of repeated injections of allergenic extracts. The questionnaire focused only on methods used for immunotherapy. Repeated subcutaneous injections for treatment of inhalant allergy is the preferred method used by both allergists and otolaryngologists and frequency of use appears to be similar. Injections to treat food allergy in addition to inhalant allergy is not in common use by these physicians (Table 6).

Sublingual administration of drops of inhalant, food or chemical extracts has been advocated as an alternative method of treating allergy. It is considered controversial because no scientific studies have been published showing that it is effective. It is clear from Table 6 that very few of the allergists and otolaryngologists surveyed in California use sublingual therapy.

Discussion

To our knowledge this is the first survey of allergy practice by allergists and otolaryngologists. It was restricted to CMA members, so the results may or may not reflect practices of nonmembers or of physicians in other specialties who include allergy in their practice.

Among the respondents, more than 75% of the allergists were certified by the American Board of Allergy and Immunology and more than 90% of the otolaryngologists were certified by the American Board of Otolaryngology/Head and Neck Surgery, indicating that the results of this survey reveal allergy practice methods used by physicians with documented proficiency in their specialties.

Skin testing is clearly the method favored by both groups of specialists for identifying specific allergens. The immediate wheal-and-erythema skin test procedure is well established as a reliable and useful test for detecting specific IgE-mediated allergies, and its rationale is consistent with current concepts of the pathophysiology of immediate hypersensitivity allergic reactions. Nevertheless, the procedure itself has never been standardized so various techniques are in use today. In general, for routine testing purposes allergists use a two-step procedure in which a cutaneous (prick or scratch) test is applied first, and for those allergens giving

TABLE 5.—*Diagnostic Tests for Initial Workup—Controversial Methods**

Test	Specialty	Percentage of Patients 0%	1-5%	6-25%	26-50%	51-75%	76-100%
Cytotoxic test—foods	Allergy	94	1	1	1	1	1
	Oto/H&N	85	10	3	0	0	1
Intracutaneous provocation-neutralization	Allergy	91	3	1	1	4	0
	Oto/H&N	86	6	4	0	0	3
Subcutaneous provocation-neutralization	Allergy	95	2	1	0	1	0
	Oto/H&N	91	1	2	0	0	5
Sublingual provocation-neutralization	Allergy	94	2	1	2	1	0
	Oto/H&N	92	0	0	0	3	4

Oto/H&N = otolaryngology/head and neck surgery

*Figures are percent of respondents in each specialty reporting frequency of usage of each method identified in the first column. Total percentage may diverge from 100% because of rounding errors.

TABLE 6.—*Immunotherapy Treatment Method**

Test	Specialty	Percentage of Patients 0%	1-5%	6-25%	26-50%	51-75%	76-100%
Subcutaneous—inhalants	Allergy	2	3	8	19	19	49
	Oto/H&N	10	4	22	8	9	47
Subcutaneous—inhalants and foods	Allergy	91	2	2	2	0	2
	Oto/H&N	78	7	6	2	2	4
Sublingual—inhalants	Allergy	95	2	2	0	0	1
	Oto/H&N	85	7	3	2	0	3
Sublingual—inhalants and foods	Allergy	92	6	2	0	0	0
	Oto/H&N	86	9	4	0	0	1
Sublingual—inhalants, foods and chemicals	Allergy	96	2	1	0	1	0
	Oto/H&N	91	6	2	0	1	0

Oto/H&N = otolaryngology/head and neck surgery

*Figures are percent of respondents in each specialty reporting frequency of usage of each method identified in the first column. Total percentage may diverge from 100% because of rounding errors.

negative reactions by this method, an intracutaneous test using a single standard concentration of extract is then applied. Serial endpoint titration is the method preferred by otolaryngologists. It consists of intradermal testing of each allergen serially at increasing concentrations until a positive (endpoint) test occurs. Our survey showed that the skin testing procedures are used by both allergists and otolaryngologists frequently in the diagnosis of inhalant allergy, but much less frequently for food allergy.

RAST, although favored more by the otolaryngologists, plays a small role in practice, since about 80% of the otolaryngologists and 90% of the allergists use this test rarely or not at all for the diagnosis of inhalant and food allergy. There is a small group of otolaryngologists who use this technique frequently.

Patients with atopic allergy usually have high circulating levels of total IgE in the serum. Because total IgE measurement affords no information about specific sensitivities, it is not surprising that fewer than 20% of physicians in either specialty order this test for most of their patients.

The controversial diagnostic techniques of cytotoxic testing and provocative-neutralization testing are not used to any significant extent by either specialty surveyed.

Treatment methods for allergen immunotherapy are similar. Subcutaneous injections are used to immunize for inhalant allergy, and very few practitioners report using immunotherapy to treat food allergy. Questions about dosage, frequency of injections, duration of treatment and patient selection criteria were not addressed in this questionnaire. The sublingual method of immunotherapy cannot be considered a significant part of the armamentarium of these physicians.

Conclusion

CMA member allergists and otolaryngologists were surveyed in 1983 to determine the methods they use for the diagnosis and treatment of allergy. These specialists generally employ similar methods in the diagnosis and treatment of allergic disease. Both groups rely on skin testing to identify specific allergens and both use a form of "titration." The otolaryngologists prefer the more formal serial intracutaneous endpoint titration method, whereas the allergists use a simplified two-step cutaneous-intracutaneous procedure. RAST is more likely to be used selectively than routinely, as is total serum IgE. The controversial diagnostic techniques of cytotoxic testing and provocation-neutralization are clearly out of favor by both groups of specialists.

Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

YAG Laser for Posterior Lens Capsules

QUESTION:

Is the use of the neodymium YAG laser for opening (disruption) posterior lens capsules after extracapsular cataract extraction considered accepted medical practice or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panel on Ophthalmology, the use of the neodymium YAG laser to open (disrupt) posterior lens capsules after extracapsular extraction is considered established medical practice. When used in the anterior segment of the eye, this procedure has been reported to be safe and effective, with an extremely low rate of complications. Indeed, because it avoids infection and other complications of conventional ocular surgery, this technique is considered a preferred alternative to surgical discission.

Although the procedure itself is considered accepted practice, not all YAG lasers have been approved by the Food and Drug Administration (FDA) for this purpose. Their use, therefore, is investigational.

Utah State Medical Association Annual Meeting

September 25-27, 1985

Westin Hotel Utah, Salt Lake City

Changes will continue to take place as "Medicine Moves Ahead in the Eighties." The meeting theme this year calls attention to the special Forum on Medical Issues which will bring together nationally prominent speakers to address issues in government, medical ethics, hospitals, and physician practice patterns.

Forum on Medical Issues

Thursday, September 26, 1985

(CME Credit 3 Hours)

Carolyne K. Davis, R.N., Ph.D.

Administrator of the Health Care Financing Administration (HCFA), Dr. Davis oversees the functions of the Medicare and Medicaid programs. HCFA helps to finance health care services for 50 million poor, elderly and disabled Americans with a budget over $90 billion in 1985.

Scott S. Parker, M.H.A.

Mr. Parker has held positions with health care institutions on both a state and national level. He is president of the American Hospital Association, a past member of the Board of Trustees, and past chairman of Associated Hospital Systems.

Ernlé W. D. Young, Ph.D.

Chaplain at the Stanford University Medical Center, Dr. Young is a senior lecturer on medical ethics. With a worldwide perspective, Dr. Young is well informed on ethical conflicts currently facing medicine.

Joseph F. Boyle, M.D.

Past president of the American Medical Association and Executive Director of ASIM. Dr. Boyle was chairman for the Health Agenda for the American People. A captivating speaker, Dr. Boyle brings to the forum the perspective of physicians and the challenges they will face in the modern medical marketplace.

Physician Reactor Panel

Following presentations by Forum speakers, questions and interaction with a physician panel will take place.

Panel Members:

Kim A. Bateman, M.D., practicing family physician and immediate past president of the Utah State Medical Association, member of the AMA Young Physicians Committee.

Alan R. Nelson, M.D., practicing physician in internal medicine, member of the AMA Board of Trustees and member of the Governing Council of the Institute of Medicine, National Academy of Sciences.

John C. Nelson, M.D., practicing obstetrician and gynecologist, member of the National Commission for review of the DRG System, member of a Steering Committee for the Health Agenda for the American People.

William D. Odell, M.D., professor of medicine and physiology, chairman of the Department of Medicine, University of Utah.

USMA House of Delegates

Wednesday, September 25, 1985

The House will commence with delegates meeting Wednesday morning for consideration of resolutions, reports and election of officers.

Reference committee meetings will also be held Wednesday morning followed by a luncheon for delegates.

Thursday, September 26, 1985

The House will reconvene to hear reports from reference committees and election results.

Special Events

Wednesday, September 25, 1985

The Hospital Medical Staff Section will meet prior to the USMA House of Delegates.

Luncheon with guest speaker:
John J. Coury, Jr., M.D.
Chairman, Board of Trustees
American Medical Association

Thursday, September 26, 1985

Luncheon with guest speaker:
Scott S. Parker, M.H.A., President
American Hospital Association

Presidents' Reception and Banquet
Lafayette Ballroom, Hotel Utah

Marketing Strategies for Private Practice

Friday, September 27, 1985

(CME Credit 2 Hours)

The business side of medical practice will be reviewed in a special AMA practice management seminar. You will learn practical ways to increase your patient load and maintain satisfaction with existing patients.

Seminar is useful for physicians just entering practice as well as those who are well established.

Course is limited to 50 participants. Cost: $75.00

Scientific Program

Friday, September 27, 1985

(CME Credit 3 Hours)

This exceptional half-day course provides a medical update on heart and vascular disease. The Scientific session is sponsored by Hoechst-Roussel Pharmaceuticals, Inc.

Cost Effective Use of Antimicrobials

Steven R. Jones, M.D.
Department of Medicine
Good Samaritan Hospital and Medical Center
Portland, Oregon

New Aspects of Treatment — Chronic Peripheral Vascular Disease

D. Eugene Strandness, M.D.
Professor of Surgery
University of Washington School of Medicine
Seattle, Washington

Use of Thrombolytic Therapy in Myocardial Infarction

William John Rogers, Jr., M.D.
Director, Myocardial Infarction Research Unit
UAB Medical Center
Birmingham, Alabama

Computer Workshops

Friday, September 27, 1985

(CME Credit 7 Hours)

Computer industry and American Medical Association surveys indicate that computer ownership by physicians will steadily increase throughout the 1980's. "User friendly" systems are rapidly developing that make office-based computer systems a necessity. USMA will present the second annual computer seminar all day on Friday, September 27. Cutting-edge information and outstanding teachers will be available for Utah physicians.

Topics will include:

Computers in Medical Practice: An Introduction
Physicians' User Panel Presentation
Computer Communication
Paperless Billing
The Paperless Office
Clinical Software
Computers in Medical Practice Made Easy
Integrated Academic Information Management System

Registration: No registration fee for USMA members
Nonmembers $50 • Thursday Luncheon $10 • Presidents' Banquet $50 per couple

For further information or registration material, please contact Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. Telephone (801) 355-7477.

(Continued from Page 181)

September 18-20—**Adolescent and Family Treatment: An Investment for the Future.** The McDonald Center for Alcoholism and Drug Addiction Treatment Center of Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Wednesday-Friday. Fee: $190. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 454-6222.

September 19-22—**International Sex Research Conference/1985 Annual Conference.** The Society for the Scientific Study of Sex, Inc. at Holiday Inn Embarcadero, San Diego. Thursday-Sunday. 14 hrs. Contact: Dwight Dixon, PhD, PO Box 9902, San Diego, 92109. (619) 276-3616.

September 23-27—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD. Monday-Friday. 13-33 hrs. Fee: $215-440.

September 26-28—**1985 Pacific Occupational Safety and Health Conference** at Le Baron Hotel, San Jose. Thursday-Saturday. Contact: Duke Hughes, POSH '85, PO Box 4420, Santa Clara, CA 95054. (408) 988-1111.

September 27-28—**40th Annual Merritt Hospital Medical Staff Seminar: Medicine, 1985.** Samuel Merritt Hospital at Kaiser Center and Merritt Hospital, Oakland. Friday-Saturday. 10 hrs. Fee: $20. Contact: Patricia R. Napp, Med. Staff Support Services, Merritt Peralta, Hawthorne Ave. & Webster St., Oakland, CA 94609. (415) 655-4000.

September 28-29—**The Skin From A to Z.** UCSF at Holiday Inn, Napa Valley. Saturday-Sunday.

September 29-October 2—**Symposium on Prevention of Osteoporosis.** University of Hawaii at Westin Ilikai Hotel, Honolulu. Sunday-Wednesday. 13.5 hrs. Fee: $300. Contact: Dr Philip Ross, Osteroporosis Center, Kuakini Medical Center, 347 N. Kaukini St., Honolulu, HI 96817. (808) 547-9578.

October 4—**One Day Dermatology Office Procedures.** Continuing Medical Education Associates at Kona Kai Club, San Diego. Friday. 7 hrs. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

October 6—**One Day Dermatology and Dermatology Office Procedures.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. 7 hrs. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

October 16—**Alcohol and Drug Symposium.** Southern California Permanente at Pasadena Hilton Hotel, Pasadena. Wednesday. Contact: Judy Harrison, Dept. of Clinical Services, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 17-20—**Clinical Biofeedback Certificate Program.** UCLA at Los Angeles. Thursday-Sunday. 24 hrs. $95.

October 17-20—**10th Annual Western Regional Meeting of the Society of Nuclear Medicine** at Palm Springs. Thursday-Sunday. Contact: Justine Parker, PO Box 40279, San Francisco, CA 94140. (415) 647-0722.

October 17-20—**Quality Care in the Workers Compensation System.** USC at Los Angeles. Thursday-Sunday. 21 hrs.

October 19-20—**Passionate Attachments: The Essential but Fragile Nature of Love.** Continuing Education Seminars at Century Plaza Hotel, Los Angeles. Saturday-Sunday. 12 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave., Los Angeles, CA 90024. (213) 475-8300.

October 25-27—**Child Abuse.** Institute for the Advancement of Human Behavior at Anaheim. Friday-Sunday. 15 hrs. $145-$225. Contact: IAHB, 4370 Alpine Road, #205, Portola Valley, CA 94025. (415) 851-8411.

October 25-29—**The Spine: Advanced Concepts and Techniques.** The Spine Study Group at Vacation Village Hotel, San Diego. Friday-Tuesday. Contact: Spine Study Group, PO Box 13185, San Diego, CA 92103. (619) 692-9115.

October 26—**Symposium on Infectious Disease: Diagnosis and Treatment in the Office Practice.** Center for Healthcare Communications at Hilton Hotel, Sacramento. Saturday. 6 hrs. Contact: Pamela Harvey, Center for Healthcare Communications, 420 Lexington Ave., #320, New York, NY 10017. (212) 210-8940.

IDAHO

August 15-17—**Sun Valley Emergency Medical Conference.** Sun Valley. Thursday-Saturday. Followed by a float trip on the Middle Fork of the Salmon River, August 18-20. Sponsors: Idaho Emergency Medical Services System; Idaho Chap, American College of Emergency Physicians; Idaho Chap, Emergency Nurses Assn; Idaho Committee on Trauma, American College of Surgeons; Rural Area Model System. Contact: Idaho EMS System, 450 W State St., Boise 83720. (208) 334-4245.

August 15-21—**Effective Diagnosis and Treatment of Infectious Diseases.** Middle Fork of the Salmon River, Idaho White Water Rafting. Thursday-Wednesday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 22-25—**Intermountain Dermatology Society.** Red Fish Lake Lodge, Idaho. Thursday-Sunday. 9½ hrs. Sponsor: University of Utah. Contact: C. David Hansen, MD, (801) 321-1100.

September 8-14—**Up-to-Date Cardiac Therapy.** Middle Fork of the Salmon River, Idaho White Water Rafting. Sunday-Saturday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

October 12-18—**Effective Diagnosis and Treatment of Infectious Diseases.** Salmon River, Idaho Sports Fishing. Saturday-Friday. 24 hrs. Cat I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

October 3-5—**Montana Medical Association Annual Meeting.** Outlaw Inn, Kalispell. Thursday-Saturday. Contact: NNA, 2012 11th Ave., Ste. 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 12-14—**Concepts and Controversies in Perinatal Care.** Albuquerque. Thursday-Saturday. 13 hrs. AMA Cat. I. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

October 4-5—**Ophthalmology for Primary Care Physicians.** Albuquerque. Friday-Saturday. Marriott Hotel. 10 hrs. AMA Cat. I. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

October 10-12—**New Mexico Cancer Symposium: Current Concepts in Cancer Management for Practicing Physicians.** Albuquerque. Thursday-Saturday. La Posada de Albuquerque. 15 hrs. AMA Cat. I. Contact: St Joseph Cancer Center, Albuquerque 87102. (505) 848-8000.

October 11-12—**First Balloon Fiesta Lung Disease Conference.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center Education Building. 9½ hrs. AMA Cat. I. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

November 1-2—**New Mexico Pediatric Society Annual Meeting—Infectious Diseases in Children.** Ruidoso. Friday-Saturday. Inn of the Mountain Gods. 8 hrs. AMA Cat. I. Contact: NM Pediatric Society, Marilyn Stark, Executive Secretary, 7605 Mountain Rd. NE, Albuquerque 87110. (505) 293-1333.

November 15-16—**New Mexico Medical Society Interim Meeting.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Contact: NM Medical Society, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

December 5-7—**New Mexico Chapter, American College of Physicians, and New Mexico Society of Internal Medicine**—Annual Meetings. Thursday-Saturday. Marriott Hotel, Albuquerque. 12 hrs. AMA Cat. I. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

OBSTETRICS AND GYNECOLOGY

October 17-19—**9th Annual Pacific NW Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion/Jantzen Beach. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

September 6-7—**Ashland Conference: Infectious Disease.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 4-5—**Fifth Annual Toxicology Conference.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

October 11-13—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

August 22-25—**Intermountain Dermatology Society** (Sponsor: University of Utah). Thursday-Sunday. Red Fish Lake Lodge, Idaho. 9.5 hrs. Contact: C. David Hansen, MD, (801) 321-1100.

September 26-27—**Utah State Medical Association Annual Meeting.** Thursday-Friday. Hotel Utah, Salt Lake City. Contact: USMA, 540 E. Fifth South, Salt Lake City 84102. (801) 355-7477.

November 8-9—**Advanced Trauma Life Support** (Sponsor: University of Utah/Utah Department of Health). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Kim Tanner, (801) 533-6608.

January 20-23—**International Biomedical Engineering Symposium** (Sponsor: University of Utah). Monday-Thursday. Salt Lake City Salt Palace. 18 hrs. Contact: Joseph Andrade, PhD, (801) 581-7236.

April 10-12—**Neurology for the Practitioner** (Sponsor: University of Utah). Thursday-Saturday. Salt Lake City Sheraton. 18 hrs. Contact: J. Richard Baringer, MD, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 26-30 (OREGON)—**Psychiatry for Primary Care Physicians.** Monday-Friday. Sunriver Resort. Contact: U/W.

September 5-6—**Microbiology Update.** Seattle. Thursday-Friday. U/W Health Sciences. Contact: U/W.

September 6-7—**Washington State Society of Anesthesiologists Fall Meeting.** Hood Canal. Friday-Saturday. Alderbrook Inn. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

September 9—**Legislative Workshop.** Yakima. Monday. Thunderbird Inn. Contact: Carole Zeigler, Washington State Hospital Association, 190 Queen Anne Avenue North, Seattle 98109. (206) 352-2526.

September 9-13—**Advances in Family Practice/ACLS.** Seattle. Monday-Friday. U/W Health Sciences. Contact: U/W.

September 19—**JCAH Update on Quality Assurance.** Seattle. Thursday. Marriott Hotel. Contact: Wendy Ray, Washington State Hospital Association, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 288)

WSMA

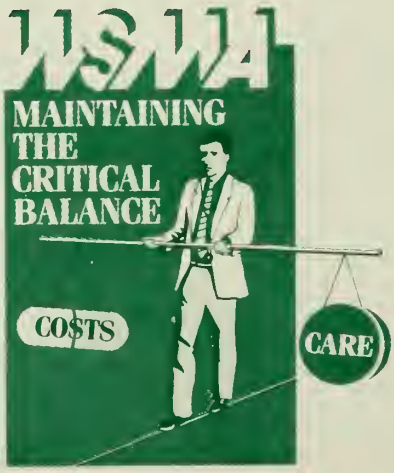
WASHINGTON STATE MEDICAL ASSOCIATION

MEETING FOCUSES ON CHANGE AND CHALLENGES

MAINTAINING THE CRITICAL BALANCE BETWEEN COSTS AND CARE will be an important theme of the 1985 WSMA Annual Meeting, September 19-22, Thunderbird Motor Inn, Jantzen Beach.

In addition to House of Delegates sessions which will shape future WSMA action on issues, including professional liability, the event-packed four-day meeting will feature a strong social-economic program and comprehensive scientific program.

All WSMA members are invited to attend.



ANNUAL MEETING
SEPTEMBER 19-22, 1985

SEPTEMBER 19-22, 1985

THUNDERBIRD MOTOR INN, JANTZEN BEACH, PORTLAND

SCIENTIFIC PROGRAMS

SURGERY	Prostate Imaging Using Transrectal Ultrasound, Plastic Surgery Symposium on Breast Reconstruction, Newer Aspects in Plastic Surgery
PSYCHIATRY	Post-traumatic Stress Disorder, Couples Therapy, WSPA Business Meeting
EMERGENCY MEDICINE	Chest Trauma in the Multiple Injury Patient, Post-Cardiac Arrest Cerebral Resuscitation, Thrombolytic Agents in Acute Myocardial Infarction, Free Standing Emergency Centers
ALLERGY	Recent Advances in Allergy and Clinical Immunology (for the non-specialist)
INTERNAL MEDICINE	Thrombolytic Therapy in Acute Myocardial Infarction, Update on AIDS, Pre-Thrombotic States and the Management of Venous Thrombosis, ACP: Health and Public Policy, ASIM Activities; An Update, Osteoporosis, Chronic Hepatitis, Flexible Sigmoidoscopy-1985, Ethics and Health Care Choices, Physician Reimbursement Issues, Rheumatology Session
OPHTHALMOLOGY	Scientific Program to be Announced, Choices for the Future of Ophthalmology, Joint Board Meeting (Washington and Oregon), Ophthalmic Assistants' Program (3 hour course on refraction)
FAMILY PRACTICE	Program to be Announced

A complete copy of the scientific program and annual meeting program is available from the Washington State Medical Association, 2033 Sixth Avenue, #900, Seattle, WA 98121, (206) 441-9762

Annual Meeting Speakers Varied, Provocative

An innovative no-fault approach to tort reform will be presented by Jeffrey O'Connell, professor of law at the University of Virginia. O'Connell specializes in accident and insurance law. He has authored numerous books including a 1979 work, "The Lawsuit Lottery: Only the Lawyers Win." O'Connell will speak to the House of Delegates on Thursday morning, 11:00 a.m.

Harry E. Morgan, Jr., chairman of the Health Care Purchasers Association of Puget Sound, will also address the House. He will discuss "A Business Prospectus on the Cost of Health Care."

Thursday afternoon Susan M. Schmidt, counsel to the special AMA Task Force on Professional Liability which has produced a series of reports on the issue, will join O'Connell and Morgan on a special reference committee panel. The panel will further review the liability issue and invite physician comment.

Dr. Roy M. Schwarz, AMA vice president of medical education and science policy, will address meeting attendees on Friday morning on the future direction of medical education and major science issues facing American medicine in the future.

If you would like additional information regarding the 96th WSMA Annual Meeting, detach and return the completed form below:

Return to:
Washington State Medical Association
2033 Sixth Avenue, #900
Seattle, WA 98121

Please send me more detailed information on the 1985 Washington State Medical Association Annual Meeting

Name

Address

City *State* *Zip*

96th ANNUAL MEETING

(Continued from Page 285)

September 19-22—**Washington State Medical Association Annual Meeting.** Jantzen Beach. Thursday-Sunday. Thunderbird Motor Inn. Contact: Patti Smith, WSMA, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

September 24—**Executive Survival and Effectiveness in a Changed Health Industry.** Seattle. Tuesday. Marriott Hotel. Contact: Wendy Ray, Washington State Hospital Association, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

September 28-October 4 (SAN JUAN ISLANDS)—**Effective Management of Common Sports Injuries.** Saturday-Friday. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (206) 788-4995.

October 2—**Update on Labor Laws.** Seattle. Wednesday. Red Lion Inn. Contact: Wendy Ray, Washington State Hospital Association, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

October 2-4—**ACP—Clinical Topics in Pulmonary Medicine.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

October 10-11—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. Westin. Contact: U/W.

October 17-18—**Washington State Hospital Association—Annual Meeting.** Seattle. Thursday-Friday. Red Lion Inn. Contact: Wendy Ray, WSHA, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

October 18—**Annual Cancer Conference.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 24-25—**Alzheimer's.** Seattle. Thursday-Friday. Westin. Contact: U/W.

October 25-26—**Neonatal and Pediatric Advanced Life Support.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

November 1—**Frontiers in Eye Care for Health Professionals.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 1-2 (VANCOUVER)—**Northwest Urological Society 1985 Annual Meeting.** Vancouver, BC. Friday-Saturday. Bayshore Inn. Contact: Patti Smith, Northwest Urological Society, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

November 7-8—**Washington Chapter, American College of Emergency Physicians—15th Annual Clinic Conference.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington Chapter, ACEP, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

November 15—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 23-30 (HAWAII)—**Medical Malpractice: Preventive Approach.** Maui. One week. Contact: U/W.

December 6—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 7-8—**Washington State Society of Anesthesiologists Winter Meeting.** Seattle. Saturday-Sunday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

December 27-January 3 (HAWAII)—**Medical Malpractice: Preventive Approach.** Maui. One week. Contact: U/W.

January 23-24—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 7-8—**Clinical Problems in Urology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 28-March 1—**Neurology—Past, Present, Future.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

March 21-22—**Medicine for Psychotherapists.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

April 5—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 2-3—**Functional Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8-9—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

WYOMING

August 26-28—**Tutorials in the Tetons: Clinical Cardiology, Diagnostic and Therapeutic Advances.** Jackson Lake Lodge, Grand Teton National Park, Moran. Monday-Wednesday. Sponsor: American College of Cardiology. Contact: ACC, Extramural Prog. Dept., 9111 Old Georgetown Rd., Bethesda, MD 20814. (301) 897-5400, ext. 230.

September 7-12—**Applications in Preventive Medicine.** Yellowstone National Park Bicycle Tour. Saturday-Friday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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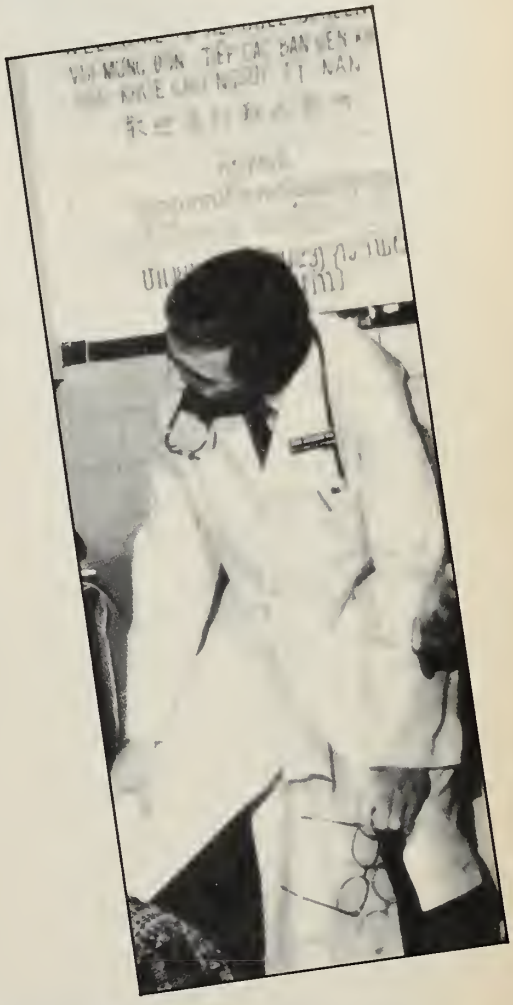

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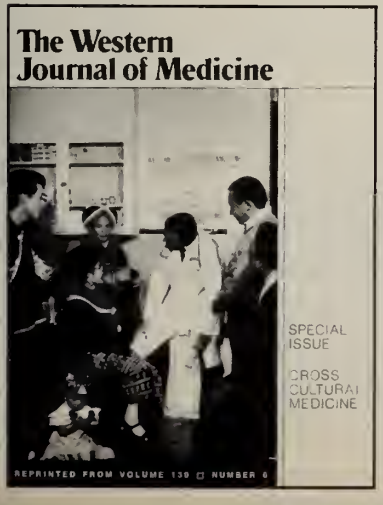

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FAMILY PRACTICE PHYSICIAN to join 15 physician multispecialty group located in Southern Idaho. Send résumé to Business Administrator, Box 1233, Twin Falls, ID 83301.

FAMILY PRACTICE opportunity in eastern New Mexico. Join two physicians in private practice situation with an established patient population. Must do OB. No buy-in; just share expenses and call. Family community with stable economy. Contact Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext. 3050.

ACADEMIC GENERAL INTERNISTS, CARDIOLOGIST, AND ENDOCRINOLOGIST, DO—Wanted for full-time faculty positions. Must be Board admissible or certified, interested in teaching medical students and house staff. Good balance between clinical practice and teaching with research opportunities available. Assistant Professor level with excellent guaranteed salary and benefits. Send CV to Victor H. Kaylarian, DO, Department of Medicine, University of Osteopathic Medicine and Health Sciences, 3200 Grand Ave., Des Moines, IA 50312. All inquiries confidential.

KETCHUM, SUN VALLEY, IDAHO: Internist, Surgeon, Pediatrician, Orthopedist in multispecialty, expanding, well-equipped clinic. Income moderate; quality of life highest. Dr Bryan Stone, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

HEMATOLOGIST-ONCOLOGIST to join Oncologist in progressive multispecialty group practice located in suburban San Francisco area. University affiliation and NCOG protocol participation encouraged. Competitive salary and benefits leading to partnership. Send résumé to Box 6479, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTICE-INTERNAL MEDICINE-SURGEON. Multispecialty clinic in Northern Idaho Panhandle. Nominal lease includes fully-equipped office and treatment suites with receptionist and janitorial services provided. Clinic includes lab, x-ray and pharmacy. Billing services available. Located in a four-season playground rich with forests, lakes, streams and wild game. Just 20 minutes from a 14-run ski resort. Attractive lifestyle. For information: (208) 784-1221, ext. 304. Mail résumé to: Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

GENERAL/ORTHOPEDIC SURGEON/FP/-INTERNIST to join multispecialty group in New Mexico. Excellent benefit package. First year salary guarantee negotiable. Well-equipped private outpatient clinic. Five minutes from new hospital. Call Mr. Miller or write 114 West 11th St., Silver City, NM 88061; (505) 388-1511, or (505) 538-2408 in evenings.

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Prestigious HMO is seeking experienced specialists and general practitioners for our facilities in Los Angeles and Orange Counties. Located in close proximity to major teaching centers, we offer the opportunity for continued professional development and rewarding clinical practice. Excellent compensation and benefits including paid malpractice, life, disability, medical and dental coverage, paid vacations, sick leave, educational leave and retirement plan. Please send CV to: Director/Physician Recruitment, CIGNA Healthplans of California, 700 North Brand Blvd., Suite 500-49, Glendale, CA 91203.

FAMILY PRACTICE at scenic Lake Chelan, WA. Join 3 other BC FPs, share call, expenses and building. Obstetrics required. Nearly new hospital. Gross 180-200K. Extensive recreational opportunities available. Practice for sale for modest negotiable amount or possibly available on a salaried basis. Contact Lake Chelan Clinic, PO Box 368, Chelan, WA 98816; (509) 682-2511.

NORTHERN CALIFORNIA: Physician, Board certified/eligible in Emergency Medicine or Family Practice, to work part-time or full-time in busy free-standing emergency center. Competitive compensation and malpractice paid. Send CV and references to Joanne Berkowitz, MD, The Emergency Center Medical Group, 4948 San Juan Ave., Fair Oaks, CA 95628.

FAMILY PRACTITIONER—TULARE COUNTY, CALIFORNIA: Board certified/eligible Family Practitioner to practice in an out-patient clinic, which includes in-patient duties, with 13 physicians. Consider a semi-rural lifestyle with cultural amenities, the Coast and the Sierra Nevada Mountains easily accessed. Salary: $81,236-$85,376 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. An Affirmative Action Employer.

CALIFORNIA—Physicians interested in fulltime practice in Urgent Care Center at Palo Alto Medical Foundation. Must be residency trained and Board Certified in FP, IM, General Surgery, Occupational Medicine or Emergency Medicine. ACLS Certified. Must be experienced in a wide variety of out-patient Medical/Surgical skills in adults and children. Occupational Medicine experience desirable. Salary, vacation, meeting time; malpractice, dental, medical, disability insurance; three year track for partnership. Available July/August 1985. For information send CV to: William E. Straw, MD, Medical Director, Urgent Care Center, Palo Alto Medical Foundation, 300 Homer Ave., Palo Alto, CA 94301. Please reply Box 6484, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PHYSICIANS WANTED

IMMEDIATE OPENING—Opportunity for Internist, Cardiologist or Family Practice to join two doctor clinic grossing near $400,000. Opportunity to buy in also. Two Surgeons and over five Family Practice Doctors who will support an Internist. Central WA; (509) 422-2600.

CALIFORNIA—Board Certified/eligible or residency trained emergency physician wanted to join 320 physician multispecialty group. Competitive salary and excellent fringe benefits. Ninety miles from Sierra skiing and San Francisco. California license required. Send curriculum vitae to Mrs. Carolyn Whelan, The Permanente Medical Group, Inc., PO Box 254999, Sacramento, CA 95825. An equal opportunity employer.

WASHINGTON COASTAL COMMUNITY serving a population of 65,000 is actively recruiting the following specialists: ENT, Urologist, Orthopedic Surgeon, General Surgeon. A variety of practice support options are available, i.e., office space, relocation assistance, etc. Enjoy the support of major West Coast Catholic Hospital System. Community has close proximity to major recreational areas and easy access to Seattle and Portland. For information send CV and references to: Nancy Friedrich, The Friedrich Group, 9284 Ferncliff North East, Bainbridge Island, WA 98110.

CALIFORNIA, RURAL AMERICAN AND OVERSEAS: Primary care physicians and OB/GYN needed for locum and permanent placements in CA, Saudi Arabia and, southwestern US. Excellent financial package, practice management and affiliation with a dynamic healthcare company. CV to: Beverly Froley, Westworld Healthcare Resources, 23832 Rockfield Rd., Lake Forest, CA 92630; (800) 847-1596.

CHAIRPERSON, DEPARTMENT OF SURGERY: The Permanente Medical Group is taking applications for the position of chairperson for the Department of Surgery at our Oakland Medical Center. The Oakland facility is a 330-bed acute care teaching hospital with a five-year general surgery residency program. The Surgery Department is composed of seven board certified general surgeons; two having completed vascular fellowships. Interested candidates must be board certified and prior experience with resident training programs preferred. Please send curriculum vitae to: Richard Brown, MD, Chairman, Search Committee, Kaiser Permanente Medical Group, Inc., 280 West MacArthur Blvd., Oakland, CA 94611.

CARDIOLOGIST: To join two busy invasive Cardiologists in the beautiful Pacific Northwest. Practice includes open heart surgery program, PTCA. Requires catheterization and all non-invasive modalities. EPS and PTCA would be a plus. Please reply with a CV to Box 6487, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

URGENT CARE CLINIC: Sacramento, CA. Full time family practice oriented emergency physician. Twelve hours/day. Gurarantee plus percentage. Malpractice provided. Minimum one year commitment. Please reply to Box 6485, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

MONTANA FAMILY PRACTICE: Have the best of both worlds. BE/BC Family Practitioner needed to establish a Department of Family Practice as part of The Billings Clinic—a 62-physician multispecialty group. Enjoy practice with or without obstetrics in a regional medical center with subspecialty backup and the cultural advantages of good schools, art, drama, symphony orchestra, etc. You and your family can enjoy the wide open spaces together. There is riding, fishing, hiking, skiing, hunting, canoeing, to name a few. This is a delightful place to raise a family. Salary leading to partnership. Contact: Paul V. Hoyer, MD, The Billings Clinic, PO Box 35100, Billings, MT 59107-5100. Telephone (406) 256-2500.

AMBULATORY CARE: Associate wanted. Prefer Board certified or eligible FP, EM, IM with interest in acute care for ambulatory/minor emergency center. Full- or part-time with flexible scheduling. Partnership possible. Contact Roger Simms, MD, at Firstcare Medical Center, 5702 North 26th, Tacoma, WA 98407; (206) 759-6655.

(Continued on Page 292)

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(Continued from Page 290)

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FACULTY MEMBER, ASSOCIATE PROFESSOR—Conduct university courses for licensed doctors and graduate medical students attempting to be certified by the State Acupuncture Board to practice herbology and acupuncture; teach subjects in technique and theory of acupuncture, practical application of herbal medicine within curriculum; deliver lectures; demonstrate acupuncture techniques; conduct research. Must be licensed Acupuncturist by the State of California. Must be able to take command of a classroom situation and transmit enthusiasm for course materials. Must possess AMD or OMD degree with one year experience in this job or one year related experience involving acupuncture treatment and therapeutics. $28,848 year. 40 hours/week. Job and interview in San Diego. Send a copy of this ad and your résumé re: job #1764 to PO Box 865, Sacramento, CA 95804, not later than 9/1/85.

CALIFORNIA, SAN JOAQUIN VALLEY: Personable BC/BP Emergency Medicine physician needed to associate with group of career Emergency Physicians in a progressive community, nonprofit hospital. Emergency Department is full department status, about 32,000 visits/year. Paramedic base station, trauma receiving hospital. Excellent support from consulting staff in all specialties including cardiac surgery. Interest in EMS desirable. Teaching position in Emergency Medicine Residency available. Generous financial arrangements with parity at two (2) years. Send CV in complete confidence to: PO Box 3893, Pinedale, CA 93650.

ONCOLOGIST BE/BC wanted for large HMO practice in northern California wine country. Reply with CV to Box 6489, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

OB/GYN: Board certified/eligible OB/GYN wanted to join fee-for-service multispecialty group on northern California redwood coast. Initial guarantee with immediate full partnership revenue participation, health and malpractice insurance. For additional information, please contact: Erika Quick, Administrator, Del Norte Medical Clinic Inc, 370 Ninth St., Crescent City, CA 95531; (707) 464-4116.

KNOWLEDGEABLE FP to be main practitioner and director of attractive, rapidly growing immediate medical care center. Guaranteed salary, plus percentage of gross (including lab x-ray and PT). Must be personable with excellent medical skills. Call Dr. Butler (213) 633-2273, 5203 Lakewood Blvd, Lakewod, CA

BC/BE PRIMARY CARE INTERNIST needed for community hospital-based teaching practice in East Los Angeles. Inpatient and office clinical and teaching responsibilities. Must qualify for medical school faculty appointment. California license. Competitive salary and benefits package. Bilingual English-Spanish preferred. Send CV to James Drinkard, MD, White Memorial Medical Group, 414 North Boyle Ave., Los Angeles, CA 90033.

FP/INTERNIST BC/BE for progressive Community Clinic in rural, coastal northern California. Join FP, Pediatrician, OB/GYN, FNP's and PA's in Family Medicine/Preventive Health practice. Salaried position with benefits, malpractice coverage. Pleasant university town, five minutes to hospital. Send CV/inquiries to Teresa Clark, Humboldt Open Door Clinic, Arcata, CA 95521; (707) 822-2957.

GENERAL INTERNAL MEDICINE SPECIALIST position open with 35 member multispecialty group. Excellent practice opportunity, full range of benefits, immediate shareholder status, all practice costs paid. For more information contact: Colin Wells, MD, Recruitment Coordinator, or David E. Graham, Associate Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401; (805) 546-5600.

IDAHO: Eight-man group seeking ninth physician. Live near skiing, fishing, hunting, and wilderness while practicing in two modern medical centers. One is a trauma center with active EMS system. Seeking experienced EM physician, preferably with administrative experience and EM certification. Competitive salary, malpractice, retirement, and other fringes. Reply PO Box 2572, Boise, ID 83701 or call (208) 322-1730.

PHYSICIANS WANTED

GENERAL PRACTITIONER needed for hospital in Northern Oregon. A basic 40 hour work week, 8 am to 5 pm per day plus rotating emergency call will be required. Salary offered is $120,000 for the first 24 months. MD degree and one year medical internship required. Interviewing and moving expenses are paid. Qualified candidates please send CV to: Employment Division, Attn: Job Order #1885172, 875 Union St. N.E., Room 208, Salem, OR 97311. Job Order #1885172.

SAN FRANCISCO (San Francisco County): Internal Medicine private practice opportunity available. Board certified/eligible, woman preferred. Practice established over 8 years, busy, excellent location in office building next to Children's Hospital, with housestaff, ER, all facilities close at hand. Versatile call schedule and opportunities for teaching available. Contact: Ann Fricker, MD, 3838 California St., Ste. 12, San Francisco, CA 94118; (415) 387-6171.

OREGON—GENERAL SURGEON sought for multispecialty group, serving 57,000 population area. Beautiful rural community, 38 miles from Portland. Send CV to ADM. Physicians' Medical Center, P.C., 420 East 5th St., McMinnville, OR 97128; (503) 472-6161.

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GASTROENTEROLOGIST BE/BC wanted for large HMO practice in northern California wine country. Reply with CV to Box 6488, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.**

SKI AND WORK—Part-time ER experienced, ACLS certified physicians sought to staff ski area clinics in Nevada, Oregon and New Mexico. Financial remuneration and benefits! Send CV to: C. H. Fagan, MD, Box 5220, Playa del Rey, CA 90296 or call (213) 546-3107 for further details.

PRACTICES AVAILABLE

CALIFORNIA BAY AREA. Primary Care for sale. Established General Practice one hour to San Francisco. Area growing very rapidly. $100,000+ gross last 5 years. Asking $50,000 but very flexible, depending on amt. of equip I leave. Please reply Box 6490, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PULMONARY DISEASE/ALLERGY practice in San Bernardino. Good lease, 1,400-foot office. Computer billing and Video patient educational systems, Pulmonary Function Laboratory equipment, trained assistant. Donald Thornton, MD, 1800 North Western Ave., 3406, San Bernardino, CA 92411; (714) 887-8088.

WELL ESTABLISHED GENERAL PRACTICE and free standing care center in Northern California for sale. Office fully equipped. Inquiries Box 6481, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

PRACTICES AVAILABLE

OB/GYN PRACTICE for sale in the Napa Valley. Solo private practice with call sharing with other OB/GYNs. $300,000 gross in 1984. 150 bed hospital with new Maternity Center. One hour from San Francisco. Available immediately. Will continue working for three to six months to assure successful transition. Contact: Lanita C. Witt, MD, 935 Trancas, Suite 4E, Napa, CA 94558; (707) 257-2571.

OPHTHALMOLOGY PRACTICE FOR SALE: 1985 or 1986. Pacific Northwest Coast. Office building for lease or sale. Retiring. Will stay to introduce. Reply including CV to Box 6472, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

CALIFORNIA: Otolaryngology, Pediatric, Psychiatric, Opthalmology, Allergy, OBG, Family, Internal, Surgery, Orthopedic, others. Contact Mary Bradshaw, Practice Broker/Recruiter, 21 Altamount Dr., Orinda, CA 94563; (415) 376-0762.

ORTHOPAEDIC PRACTICE—Orange County, California, adjacent to major hospital; five additional hospitals in 5-mile radius; will aid in transition. Box 4191, Irvine, CA 92714.

SAN DIEGO—General Surgeon, OB/GYN, MD to take prac/office. Best med area. Off sublease. 2 cnslt 2 exam lg rcrds rm bath etc. Frn/equip avail. (619) 287-0151 or PO Box 202053, San Diego, CA 92120-0925.

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SAN LEANDRO: Prime, central. Prestige medical building. Ample parking. *Great* opportunity Internist or GP. Carol Bull, (415) 357-8940.

CENTRAL CALIFORNIA Arroyo Grande. Long term leasehold space with option to buy. 2,000+ square feet in new professional complex. Available in October. Help design interior now. Construction allowance given. (213) 649-0036.

AVAILABLE NOW—Oxnard, Ventura County, California; newly constructed 3,458 square feet with seven exam rooms, three consultation, x-ray, physical therapy, minor surgery, laboratory, nurses station. Contact: Anna Bischof, (805) 485-3193.

VALLEJO, CALIFORNIA: Prelease space in this new medical office building to be constructed across the street from Sutter Hospital. Sutter is doing a 13 million dollar expansion to the present hospital, to include 51 new beds, doubling the intensive care unit and adding to the surgery section. Marine World Africa USA is under construction within one mile bringing more growth to the area. Vallejo is halfway between Sacramento and San Francisco; it's convenient to skiing, the ocean and lake water sports. Building can be ready for occupancy in six months. Call Joe Lillis at (707) 864-8524 or write PO Box 523, Fairfield, CA 94533 for more information.

SITUATIONS WANTED

RADIOLOGIST SEEKS POSITION—41-year-old experienced Radiologist (academics and private practice) seeks multispecialty group, solo-type practice, or imaging center. Reply Box 6486, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: 1986: date and place to be announced.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting 1986: date and place to be announced.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1986: date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1986: date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1986: date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1986: date and place to be announced.

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

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Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine. Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

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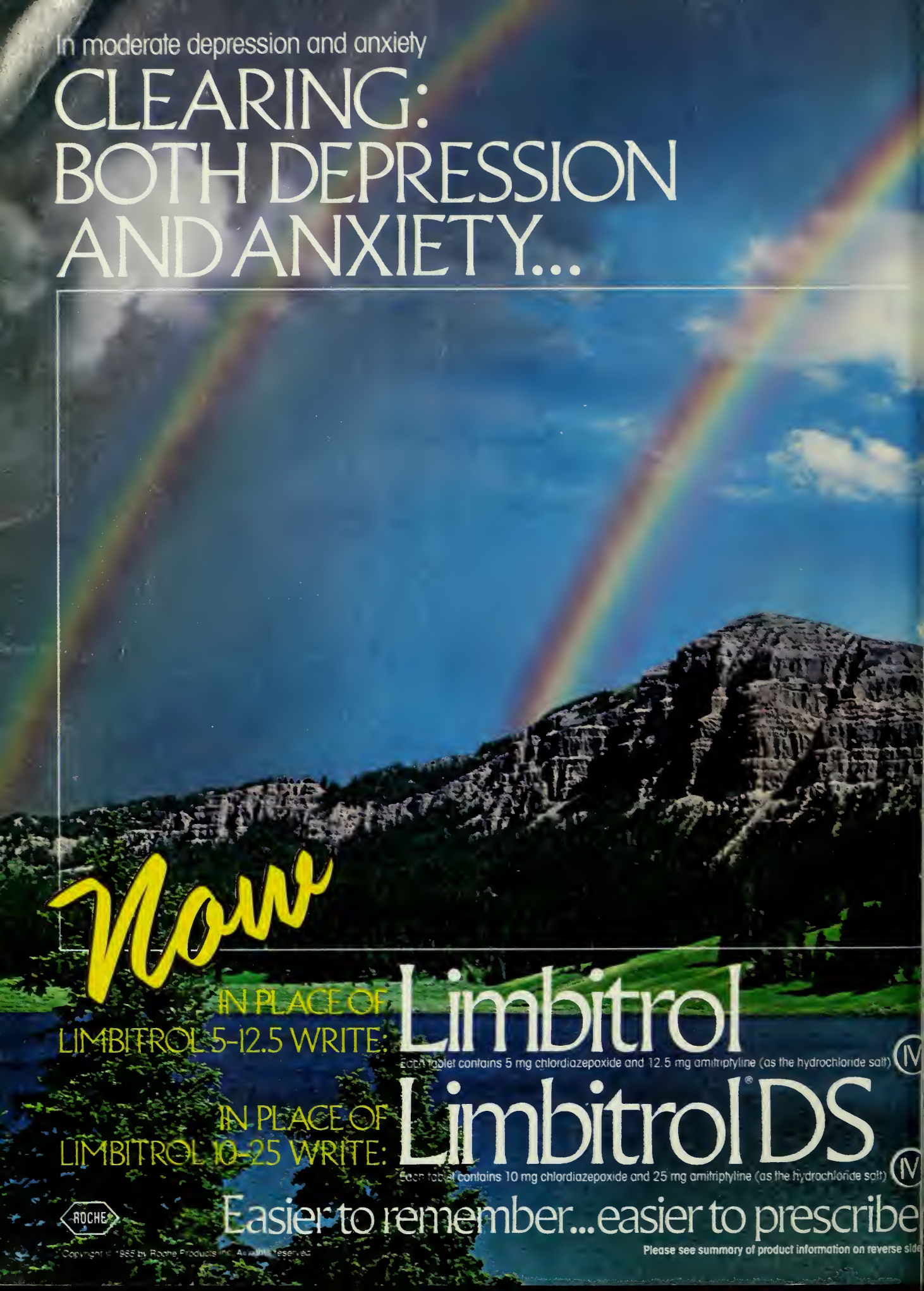

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Excellent clinical activity—and economical

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Bactrim is indicated in acute otitis media due to susceptible organisms when it offers an advantage over other antimicrobials. Bactrim is contraindicated in pregnancy, lactation, infants under two months of age and documented megaloblastic anemia due to folate deficiency. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age.

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References: 1. Klimek JJ *et al: J Pediatr* 96:1087-1089, Jun 1980. **2.** Schwartz RH *et al: Rev Infect Dis* 4:514-516, Mar-Apr 1982. **3.** Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976. **4.** Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. **5.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **6.** Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. **7.** *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981.

Please see summary of product information on the following page.

References: 1. Klimek JJ *et al: J Pediatr* 96:1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Dis* 4:514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. 7. *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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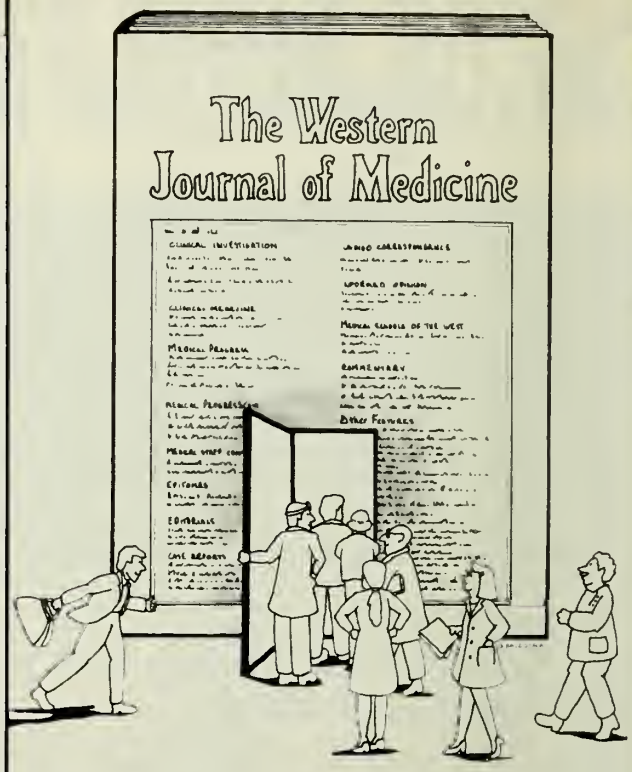

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SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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See previous page for brief summary of prescribing information.

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CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g. chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy—In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia. The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527D)

References: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Min Electrolyte Metab 8:237-254, 1982. 2. Danesh BJZ, et al: Comparison between short-term renal haemodynamic effects of propranolol and nadolol in essential hypertension: a cross-over study. Clin Sci 67:243-248, 1984. 3. Hollenberg NK: Introduction: β-adrenergic blocking agents—the treatment of hypertension and the kidney. Royal Soc of Med Int Congress and Symposium Series 51:1-8, 1982. 4. Frohlich ED, et al: Long-term renal hemodynamic effects of nadolol in patients with essential hypertension. Am Heart J 108:1141-1143, 1984. 5. Alexander JC, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

RENALLY REFERENCED LOT

SQUIBB

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Since with increasing blood pressure there may be a progressive decline in renal blood flow,[1] prescribe . . .

CORGARD® (nadolol tablets)

Lowers blood pressure

Preserves renal blood flow

Studies prove that CORGARD (nadolol tablets) preserves renal blood flow unlike some beta-blockers, such as propranolol.[1-4]

In a two-year study of 106 patients, CORGARD also decreased serum creatinine, a measurement of improved renal function.[5]

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(nadolol tablets)

STEP-1 FOR HYPERTENSION WITH ONCE-A-DAY DOSE

*For a discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary of prescribing information on adjacent page.

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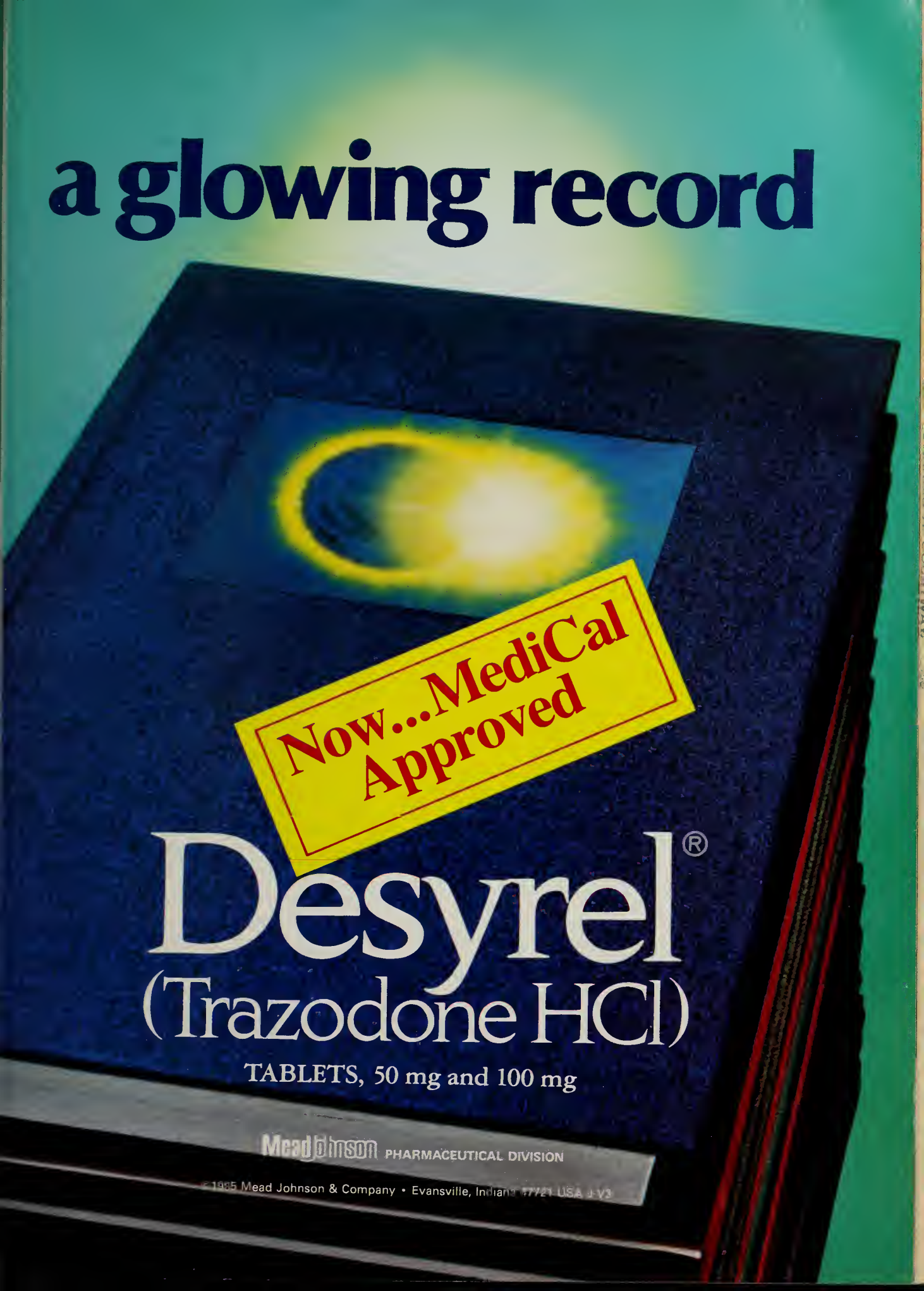
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Now...MediCal Approved
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a glowing record of acceptance

Desyrel®
(trazodone HCl)

TABLETS: 50 mg, 100 mg, 150 mg

DESCRIPTION

DESYREL® (trazodone hydrochloride) is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is a triazolopyridine derivative designated as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3-(2H)-one hydrochloride. DESYREL is a white odorless crystalline powder which is freely soluble in water. Its molecular weight is 408.3. The empirical formula is $C_{19}H_{22}ClN_5O \cdot HCl$.

INDICATIONS AND USAGE

DESYREL® (trazodone hydrochloride) is indicated for the treatment of depression. The efficacy of DESYREL has been demonstrated in both inpatient and outpatient settings and for depressed patients with and without prominent anxiety. The depressive illness of patients studied corresponds to the Major Depressive Episode criteria of the American Psychiatric Association's Diagnostic and Statistical Manual, III.[a]

CONTRAINDICATIONS

DESYREL is contraindicated in patients hypersensitive to DESYREL.

WARNINGS

TRAZODONE HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN APPROXIMATELY 1/3 OF THE CASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A PORTION OF THESE CASES, PERMANENT IMPAIRMENT OF ERECTILE FUNCTION OR IMPOTENCE RESULTED. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS SHOULD IMMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

Recent clinical studies in patients with pre-existing cardiac disease indicate that DESYREL may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, and in two patients short episodes (3-4 beats) of ventricular tachycardia. Until the results of prospective studies are available, patients with pre-existing cardiac disease should be closely monitored particularly for cardiac arrhythmias. There have also been post-introduction reports of arrhythmias in DESYREL-treated patients, some of whom did not have pre-existing cardiac disease. DESYREL is not recommended for use during the initial recovery phase of myocardial infarction.

PRECAUTIONS

General: The possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Therefore, prescriptions should be written for the smallest number of tablets consistent with good patient management. Hypotension, including orthostatic hypotension and syncope, has been reported to occur in patients receiving DESYREL. Concomitant administration of antihypertensive therapy with DESYREL may require a reduction in the dose of the antihypertensive drug. Little is known about the interaction between DESYREL and general anesthetics, therefore, prior to elective surgery, DESYREL should be discontinued for as long as clinically feasible. As with all antidepressants, the use of DESYREL should be based on the consideration of the physician that the expected benefits of therapy outweigh potential risk factors. **Information for Patients**: Alert patients that (a) because priapism has been reported to occur in patients receiving DESYREL, patients with prolonged or inappropriate penile erection should immediately discontinue the drug and consult with the physician, (b) their mental or physical ability to perform potentially hazardous tasks, such as operating machinery or driving, may be impaired, (c) the response to CNS depressants such as alcohol or barbiturates may be enhanced, and (d) DESYREL should be taken shortly after a meal or light snack. **Laboratory Tests**: WBC and differential counts are recommended for patients who develop fever, sore throat or other signs of infection. Discontinue DESYREL if WBC or absolute neutrophil count falls below normal. **Drug Interactions**: Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving DESYREL (trazodone hydrochloride) concurrently with either of those two drugs. Since it is not known whether an interaction will occur between DESYREL and MAO inhibitors, therapy should be initiated cautiously with a gradual increase in dosage until optimum response is achieved, if a MAO inhibitor is discontinued shortly before or is to be given concomitantly with DESYREL. **Therapeutic Interactions**: Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving DESYREL in daily oral doses up to 300 mg/kg for 18 months. **Pregnancy**: Since there are no adequate and well-controlled studies in pregnant women, DESYREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers**: Since DESYREL and/or its metabolites have been found in the milk of lactating rats, caution should be exercised when DESYREL is administered to a nursing woman. **Pediatric Use**: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Clinical Trial Reports: Side effects reported by more than 1% of the patients during clinical trials are the following. **Autonomic**—blurred vision, constipation, dry mouth. **Cardiovascular**—hypertension, hypotension, shortness of breath, syncope, tachycardia, palpitations. **CNS**—anger, hostility, confusion, decreased concentration, disorientation, dizziness/light-headedness, drowsiness, excitement, fatigue, headache, insomnia, impaired memory, nervousness. **Gastrointestinal**—abdominal/gastric distress, bad taste in mouth, diarrhea, nausea/vomiting. **Musculoskeletal**—musculoskeletal aches/pains. **Neurological**—incoordination, paresthesia, tremors. **Sexual Function**—decreased libido. **Skin**—allergic condition/edema, and **Other**—decreased appetite, eyes red/tired/itching, head full/heavy, malaise, nasal sinus congestion, nightmares/vivid dreams, sweating/clamminess, tinnitus, weight gain, weight loss. Side effects reported by less than 1% of the study patients are the following: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusions, hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, and retrograde ejaculation. **Post Introduction Reports**: Voluntary reports received since market introduction include the following: agitation, apnea, diplopia, edema, grand mal seizures, hallucinations, hemolytic anemia, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequently), paresthesia, priapism (see PRECAUTIONS, Information for Patients, some patients have required surgical intervention), rash, weakness. Cardiovascular system effects which have been reported are the following: orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including ventricular tachycardia (see WARNINGS).

OVERDOSE

Signs and Symptoms: Death from overdose has occurred in patients ingesting DESYREL (trazodone hydrochloride) and other drugs concurrently (namely, alcohol, alcohol + chloral hydrate + diazepam, amobarbital, chlordiazepoxide, or meprobamate). The most severe reactions reported to have occurred with overdosage of DESYREL alone have been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. DESYREL should be taken shortly after a meal or light snack. **Usual Adult Dosage**: An initial dose of 150 mg/day in divided doses is suggested. dose may be increased by 50 mg/day every three to four days. The maximum dose outpatients usually should not exceed 400 mg/day in divided doses. Inpatients may given up to but not in excess of 600 mg/day in divided doses. **Maintenance**: Dosage during prolonged maintenance therapy should be kept at t lowest effective level. Once an adequate response has been achieved, dosage may gradually reduced, with subsequent adjustment depending on therapeutic respon

HOW SUPPLIED

DESYREL® (trazodone hydrochloride) 50 mg and 100 mg scored tablets, and 150 m DIVIDOSE® tablets.

CAUTION: Federal law prohibits dispensing without a prescription.

REFERENCES

a. Williams JBW, Ed. Diagnostic and statistical manual of mental disorders-III, American Psychiatric Association, May 1980.

U.S. Pat. No. 4,215,104

Date of Latest Revision: July

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

September 13 —**Advances in Fetal Echocardiography '85.** St. Joseph's Hospital and Medical Center, Phoenix. Friday. Contact: CME and Outreach Department, St. Joseph's Hospital and Medical Center, (602) 285-3000.

September 21—**Gastroenterology.** Phoenix. Saturday. Contact: U of A.

October 12—**Practical Approach to Fluid and Electrolytes.** Tucson. Saturday. Contact: U of A.

October 18-19—**Geriatric Medicine.** Boswell Memorial Hospital, Sun City. Friday-Saturday. Contact: Western Division, American Geriatrics Society, (602) 977-1877.

October 25-26—**Therapeutic Advances: New Choices for Medical Management of Disease.** Poco Diablo Resort, Sedona. Friday-Saturday. Contact: U of A.

November 1-3—**5th Annual Southwestern Poison Symposium.** Loews Ventana Canyon Resort, Tucson. Friday-Sunday. Contact: U of A.

November 9—**Cardiology.** Phoenix. Saturday. Contact: U of A.

November 15-16—**Arizona Chapter, American College of Surgeons.** Loews Ventana Canyon Resort, Tucson. Friday-Saturday. Contact: U of A.

November 25-27—**Cemented Versus Uncemented Revision Total Joint Arthroplasty.** Registry Resort, Scottsdale. Monday-Wednesday. Contact: Medical Meetings Department, St. Luke's Medical Center, (602) 251-8402.

December 7—**Psychiatry.** Tucson. Saturday. Contact: U of A.

CONTACT INFORMATION

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 95724. (602) 626-6173.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

October 5—**Allergy of Ears, Nose and Sinuses.** Los Angeles Society of Allergy and Clinical Immunology

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KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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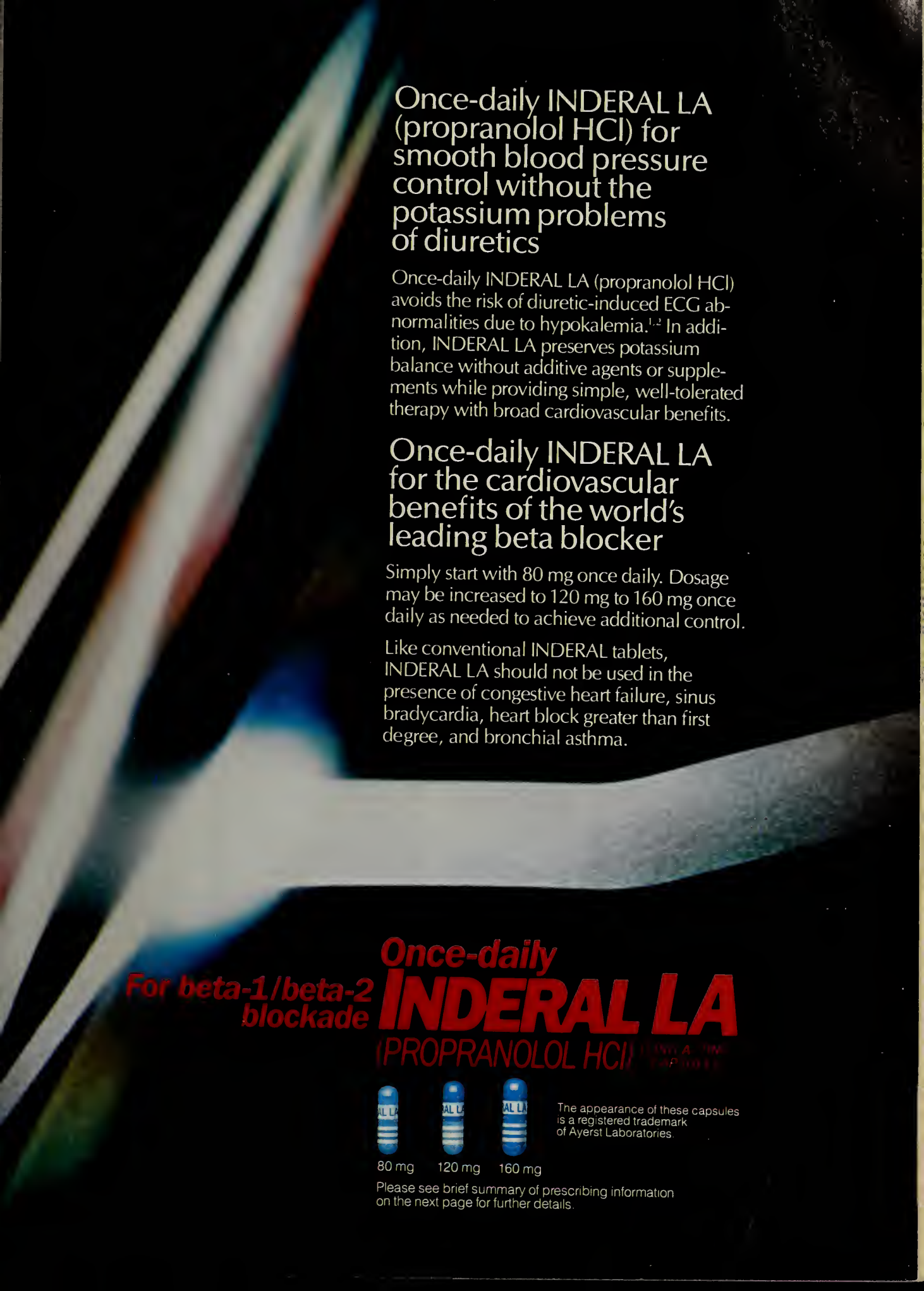

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Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[1,2] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily INDERAL LA

(PROPRANOLOL HCl)

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Please see brief summary of prescribing information on the next page for further details.

"When it comes to cardiovascular medicine, I like to know exactly what my patients are swallowing."

INDERAL® Tablets

BRAND OF PROPRANOLOL HCl

10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block; hypotension, paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Geri Coldewey, LASACI, 1626 N. Wilcox, #557, Hollywood, CA 90028.

October 16-19—**Rheumatology and Clinical Immunology: An Advanced Course.** UCSF at Hotel Meridien, San Francisco. Wednesday-Saturday. 19 hrs. $225-$375.

October 25—**Current Treatment of Allergy.** PMC at San Francisco. Friday.

ANESTHESIOLOGY

September 27-29—**Anesthesia Practice, 1985.** Anesthesiology Educational Foundation at Monterey. Friday-Sunday. 10.5 hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles, CA 90024.

October 17-26—**1985 Post ASA Annual Meeting in Hawaii.** California Society of Anesthesiologists at Hotel Intercontinental, Maui, HI. Thursday-Saturday. 24 hrs. Contact: Linda P. Londerville, CSA, 100 S. Ellsworth, #806, San Mateo, CA 94401. (415) 348-1407.

November 2—**Annual Anesthesiology Symposium.** Southern California Permanente Medical Group at Westin South Coast Plaza Hotel, Costa Mesa. Saturday. Contact: Lilia M. Guerrero, Southern California Kaiser Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

CANCER

October 21-23—**9th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. 22 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 453-6222.

November 7-8—**New Directions in Antiviral Chemotherapy.** UCSF at Holiday Inn Golden Gateway, San Francisco. Thursday-Friday.

CARDIOLOGY

September 19-21—**Echocardiography Technologist Certification Review.** The Institute for Medical Studies at Los Angeles. Thursday-Saturday. Contact: Kim Stroich, IMS, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 495-4499.

September 21—**Pulmonary Medicine.** UCSF at Fresno. Saturday.

September 26-28—**Cardiology Update, 1985.** American College of Cardiology at Quail Lodge, Carmel. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

September 30-October 4—**Comprehensive Review in Vascular Surgery** UCLA at Miramar Sheraton, Santa Monica. Monday-Friday. 32 hrs.

October 3-5—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday. 17 hrs. $150-$325.

October 4-5—**Mycology Review.** STAN at Stanford. Friday-Saturday. 14 hrs.

October 5—**8th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. Contact: Sandra Rozzen, Northridge Hospital, 18300 Roscoe Blvd., Northridge, CA 91328. (818) 885-5311.

October 5—**Artificial Heart and Heart Transplantation: An Overview.** Northridge Hospital at Century Plaza. Los Angeles. Saturday. 8 hrs. Contact: Northridge Hospital Medical Center, Northridge, (818) 885-5311.

October 18-20—**Interventional Cardiology.** The Institute for Medical Studies at Las Vegas. Friday-Sunday. 15 hrs. Fee: $375. Contact: Kim Stroich, Program Coordinator (714) 495-4499.

October 20-27—**Cardiology for the Practitioner.** UCSF at The Ahwahnee Hotel, Yosemite Lodge. One Week. Contact: Sharon Balestra Program Representative (209) 225-6100 ext. 562.

October 25-27—**International Symposium in the Aortic Root.** Scripps Clinic and Research Foundation at Hotel Del Coronado, San Diego. Friday-Sunday. 23 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 453-6222.

November 1-3—**Current Approaches to Vascular Disease.** UCSD at San Diego. Friday-Sunday. Fee: $175. Contact: Mary J. Ryals, PO Box 610203, DFW Airport, TX 75261-0203. (214) 659-9590.

EMERGENCY MEDICINE

September 23-27—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD at San Diego. Monday-Friday. 13-33 hrs. $215-$440.

September 24-26—**Postgraduate Institute for Emergency Physicians: Advanced Procedures Laboratory.** UCSD at San Diego. Tuesday-Thursday. 3 hrs. Fee: $250.

September 27—**Pain and Ethics in the Emergency Department.** Cedars-Sinai Medical Center at Los Angeles. Friday. Contact: Lore Kahane, Coordinator, Continuing Medical Education, Cedars-Sinai Medical Center, Room 2049, PO Box 48750, Los Angeles 90048. (213) 855-5547.

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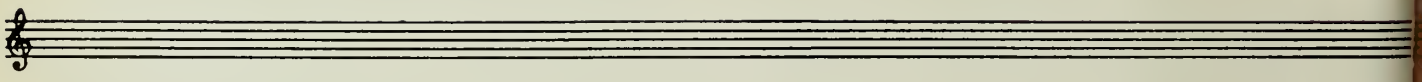

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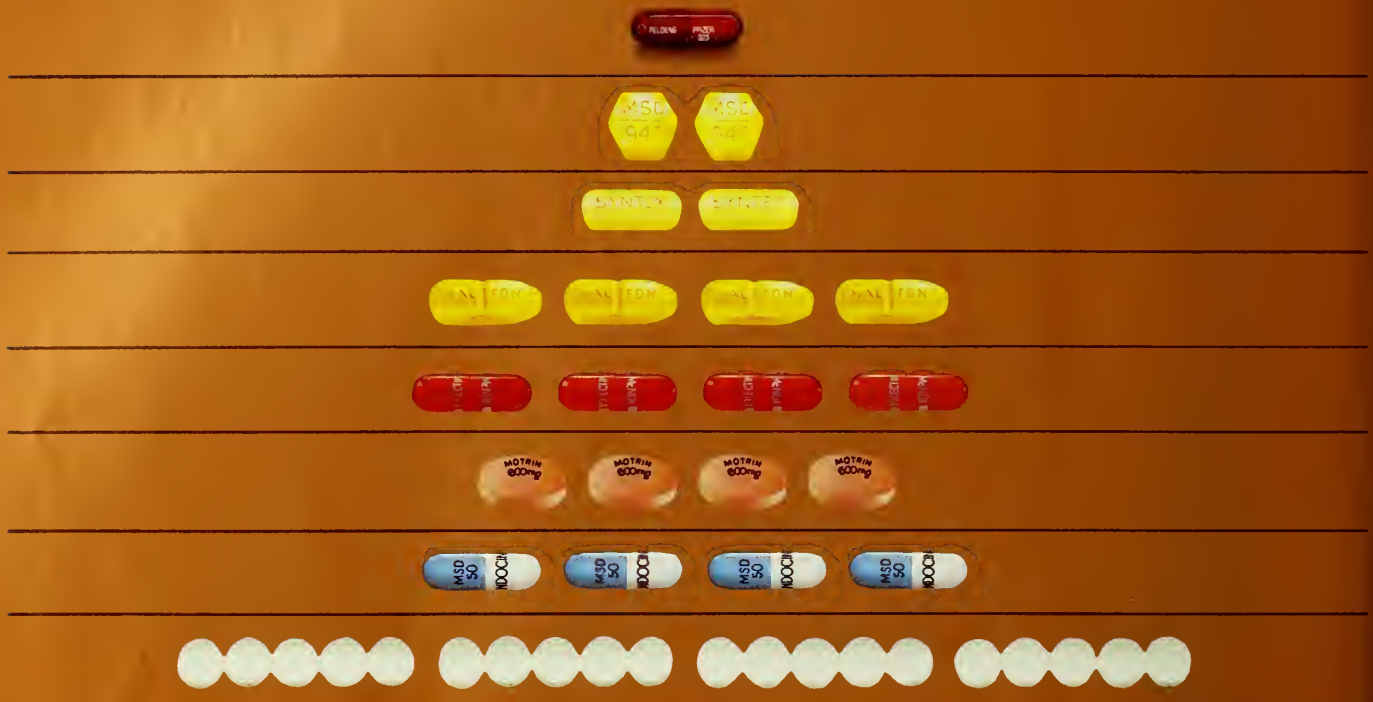

Source: PDR, 1985; Manufacturers' Prescribing Information

Indicates maximum dosage for osteoarthritis and rheumatoid arthritis for the antiarthritic agents included. Consult manufacturers' prescribing information.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice and dogs.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with FELDENE. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress*, nausea*, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia.

Dermatologic: pruritus, rash.

Central Nervous System: dizziness, somnolence, vertigo.

Urogenital: BUN and creatinine elevations (see PRECAUTIONS).

Body as a Whole: headache, malaise.

Special Senses: tinnitus.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

* Reactions occurring in 3% to 9% of patients treated with FELDENE (piroxicam).

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth.

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis.

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions.

Central Nervous System: depression, insomnia, nervousness.

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS).

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS).

Special Senses: swollen eyes, blurred vision, eye irritations.

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina.

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease.

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness", sis (see PRECAUTIONS).

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis.

Dermatologic: onycholysis, loss of hair.

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias.

Urogenital System: dysuria.

Body as a Whole: weakness.

Cardiovascular/Respiratory: palpitations, dyspnea.

Hypersensitivity: positive ANA.

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in man have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis: It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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References: 1. Siegmeth W: Serum concentrations of piroxicam in relation to its clinical effect in patients with chronic polyarthritis. *Wien Med Wochenschr* (special issue) 31-35, 1980. 2. Tausch G: Placebo controlled study of piroxicam in the treatment of rheumatoid arthritis. *Am J Med* (report) 72:18-22, February 1982. 3. Fogari R: Quality of life as a measure of therapeutic response. *Int Med* (special suppl) 37-43, 1984.

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"Information for Authors"—A complete guide to manuscript submission and journal style is available on request and also appears in January and July.

Author Responsibility—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

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Clinical Investigation—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter.

PUBLISHER

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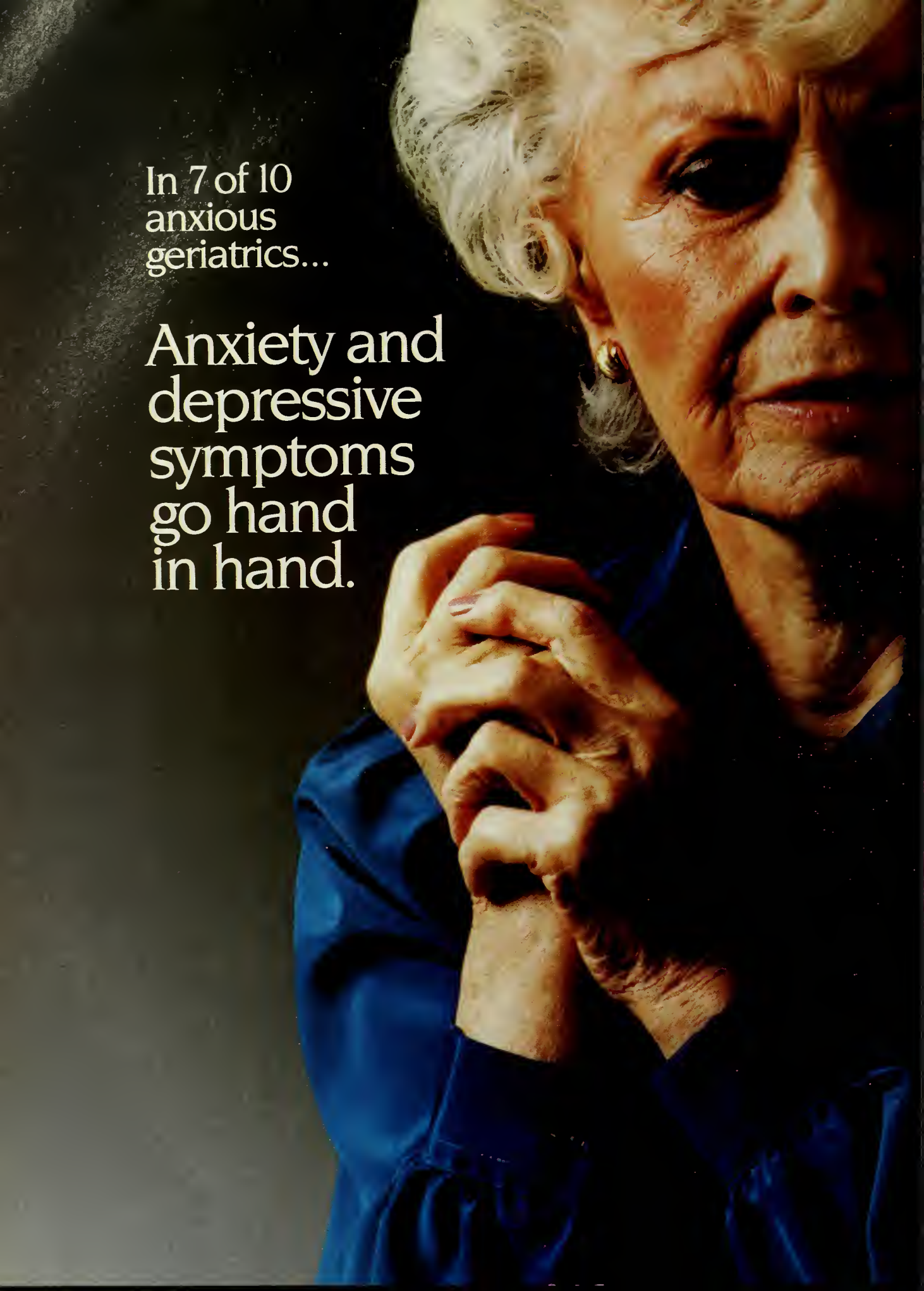
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geriatrics...
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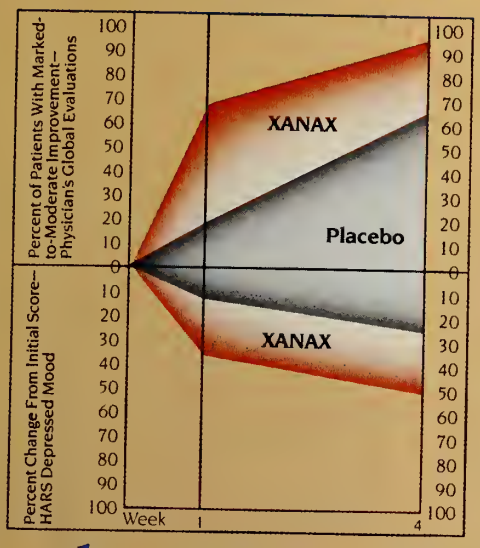

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

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1 Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112.

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Please see next page for brief summary of prescribing information.

XANAX® Tablets
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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

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CONTINUING MEDICAL EDUCATION

(Continued from Page 309)

October 3-6—**Emergency Medicine: Challenging Clinical Problems.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Thursday-Sunday.

October 4-6—**Update in Emergency Medicine.** Mercy Medical Center at Napa Valley. Friday-Sunday. 10 hrs. $125. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding, CA 96099-6009. (916) 243-2131.

October 16-20—**Traumatic Head Injury.** UCD at Red Lion Motor Inn, Sacramento. Wednesday-Sunday.

October 28-November 1—**Postgraduate Institute for Emergency Physicians: Symposium III.** UCSD at San Diego. Monday-Friday. 13-33 hrs. $215-$440.

October 30—**Postgraduate Institute for Emergency Physicians: Advanced Procedures Laboratory.** UCSD at San Diego. Wednesday. 3 hrs. $250.

INTERNAL MEDICINE

September 20-21—**Internal Medicine Symposium.** Southern California Permanente Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. Contact: Judy Harrison, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

September 30-October 2—**Frontiers in Clinical Nephrology 1985.** UCLA at Mission Inn, Sonoma. Monday-Wednesday. 22 hrs. $395.

October 7-9—**GI Board Review.** USC at Los Angeles. Monday-Wednesday. 21.5 hrs.

October 12-19—**Gastroenterology: A Review.** International Conferences at Hawaii. One week. 20 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

October 17-19—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday.

October 17-20—**Practical Advances in Internal Medicine.** UCD at Napa Valley Holiday Inn, Napa. Thursday-Sunday.

October 18-20—**Practice Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** Continuing Medical Education Associates at Vacation Village, San Diego. Friday-Sunday. 20 hrs. $295. Contact: J. Shiller, CMEA, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

October 28-29—**Gynecological Histopathology.** Memorial Medical Center and UC Irvine, at Newport Beach Sheraton. Monday-Tuesday. 19 hrs. Contact:

Sharon Richard, Program Coordinator Continuing Medical Education, Memorial Medical Center, Irvine.

November 4-6—**Internal Medicine.** UCSF at Yosemite. Monday-Wednesday.

November 9—**Endocrinology.** UCSF at Fresno. Saturday. Contact: Sharon Balestra, Program Representative. Extended Programs in Medical Education. (209) 225-6100, ext. 562.

November 9-11—**Realistic Endocrinology in Primary Care.** Merritt-Peralta Health Education Center at Oakland. Saturday-Monday. Contact: Merritt-Peralta Health Education, 400 Hawthorne Ave., Oakland 94609. (415) 420-6161.

OB/GYN

September 21—**OB/GYN.** UCSF at Fresno. Saturday. Contact: Sharon Balestra, Program Representative. Extended Programs in Medical Education. (209) 255-6100, ext. 562.

September 28—**Clinical Ultrasound—Update and Ob/Gyn.** Sacramento Radiology Research and Education Foundation at Sacramento. Saturday. 6 hrs. Fee: $50-$75. Contact: SRREF, PO Box 19184, Sacramento, CA 95819.

October 28-November 2—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** Memorial Medical Center at Sheraton, Newport. Monday-Saturday. 42-46 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

October 30-November 2—**8th Annual Review Course in Clinical Obstetrics and Gynecology.** Memorial Medical Center at Irvine. Wednesday-Saturday. 27 hrs. Contact: Sharon Richard, Program Coordinator, Continuing Medical Education, Memorial Medical Center UC, Irvine.

November 11-15—**15th Annual Review of Obstetrics and Gynecology.** USC at Hilton Hotel, Pasadena. Monday-Friday. Fee: $500. Contact: USC.

November 16—**Review Course for Gynecologic Pathology.** USC at Hilton Hotel, Pasadena. Saturday. Fee: $90. Contact: USC.

OPHTHALMOLOGY

September 29-October 4—**American Academy of Ophthalmology Annual Meeting** at San Francisco. Sunday-Friday. Contact: AAO, PO Box 7424, San Francisco, CA 94120. (415) 921-4700.

(Continued on Page 326)

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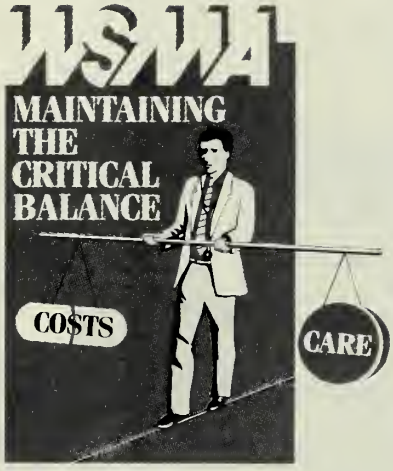

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SEPTEMBER 19-22, 1985

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An innovative no-fault approach to tort reform will be presented by Jeffrey O'Connell, professor of law at the University of Virginia. O'Connell specializes in accident and insurance law. He has authored numerous books including a 1979 work, "The Lawsuit Lottery: Only the Lawyers Win." O'Connell will speak to the House of Delegates on Thursday morning, 11:00 a.m.

Harry E. Morgan, Jr, Chairman of the Health Care Purchasers Association of Puget Sound, will also address the House. He will discuss "A Business Prospectus on the Cost of Health Care."

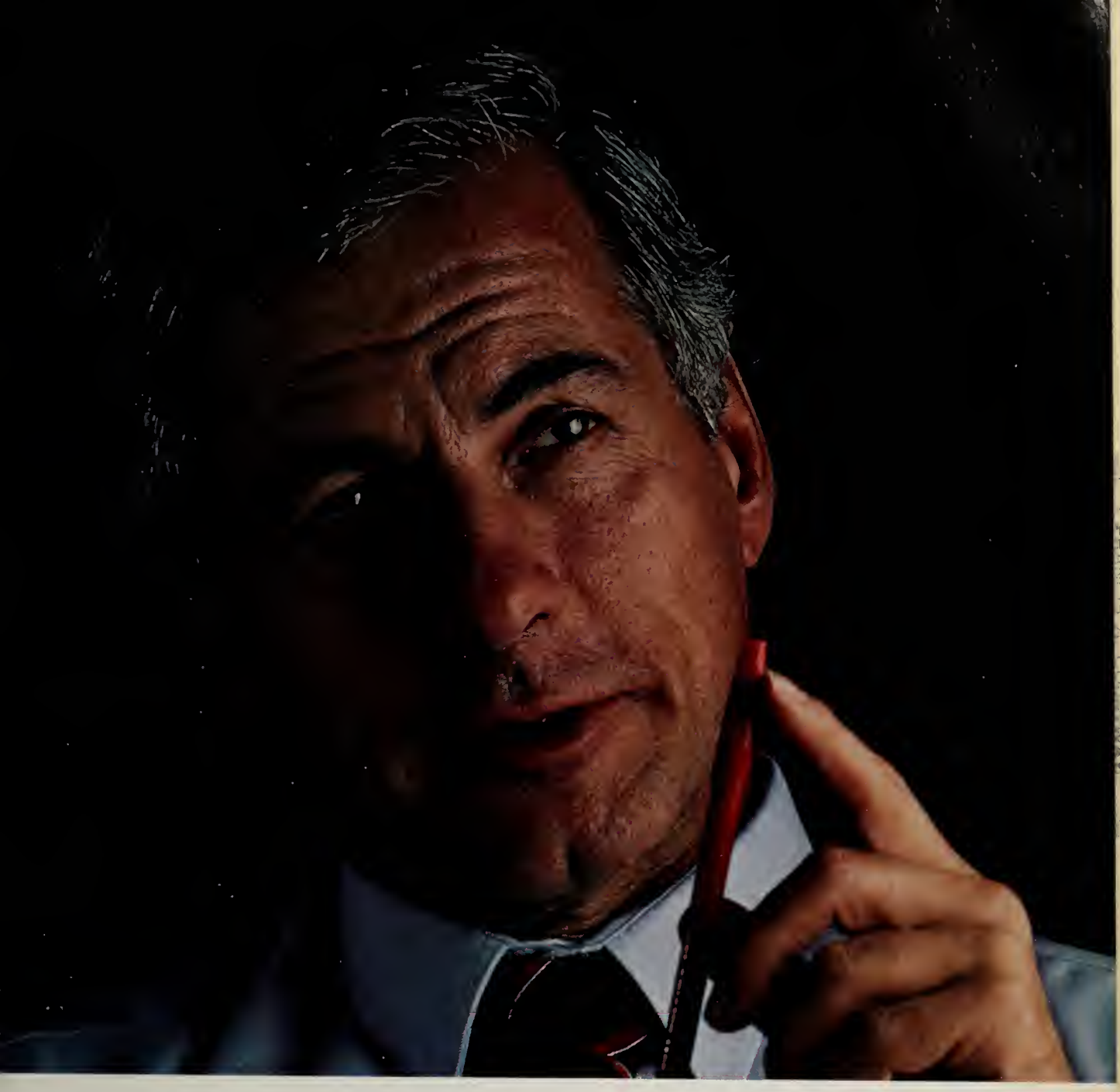
Thursday afternoon Susan M. Schmidt, counsel to the special AMA Task Force on Professional Liability which has produced a series of reports on the issue, will join O'Connell and Morgan on a special reference committee panel. The panel will further review the liability issue and invite physician comment.

Dr Roy M. Schwarz, AMA vice president of medical education and science policy, will address meeting attendees on Friday morning on the future direction of medical education and major science issues facing American medicine in the future.

Meeting Focuses on Change and Challenges

Maintaining the critical balance between costs and care will be an important theme of the 1985 WSMA Annual Meeting. In addition to House of Delegates sessions which will shape future WSMA action on issues, including professional liability, the event-packed four-day meeting will feature a strong social-economic program and comprehensive scientific program.

For further information, please contact:
Washington State Medical Association
2033 Sixth Avenue, #900, Seattle, WA 98121, (206) 441-9762



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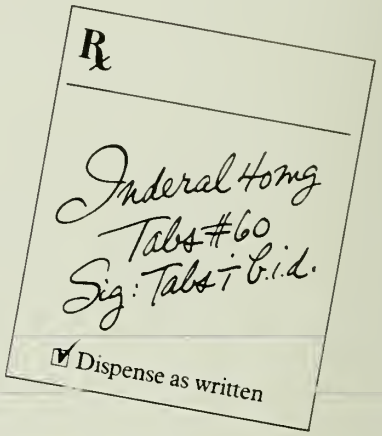

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block; hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia. LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

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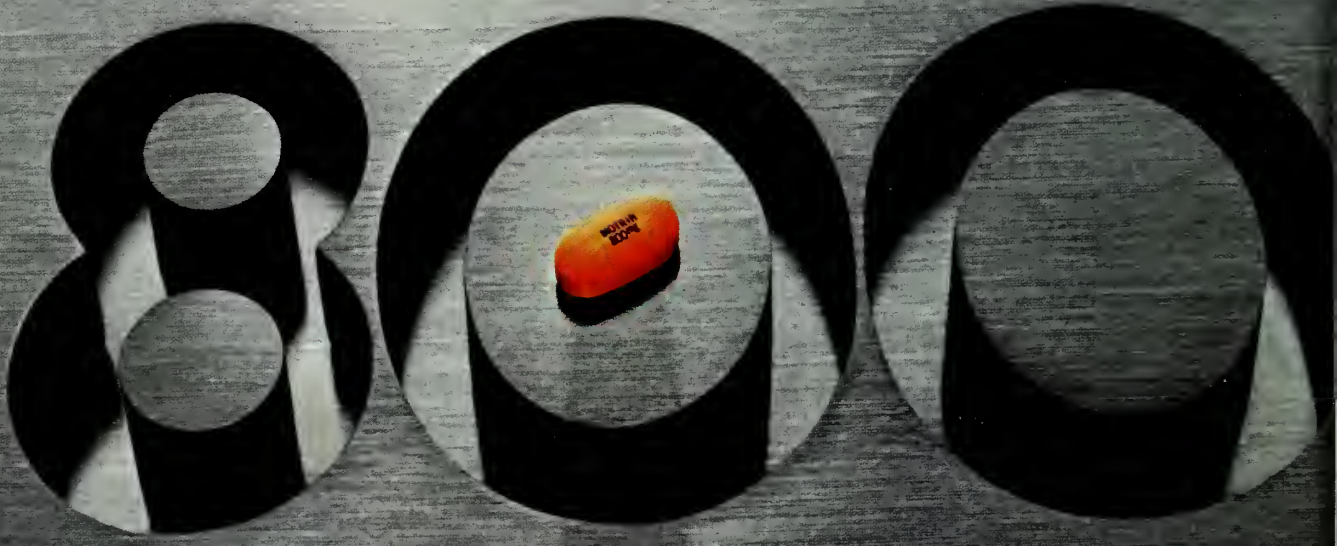

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provides economy...patients should pay less for MOTRIN Tablets than comparable dosages of Clinoril, Feldene, or Naprosyn.

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The Upjohn Company, Kalamazoo, Michigan 49001

Motrin® Tablets
(ibuprofen)
Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis. Relief of mild to moderate pain and primary dysmenorrhea. Safety and efficacy in children are not established.
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with MOTRIN.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.
MOTRIN can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, blurred vision, skin rash, weight gain, or edema. Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when MOTRIN is added.
The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGDT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (eg, eosinophilia, rash, etc.), MOTRIN should be discontinued.
In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.
Drug interactions—*Aspirin:* used concomitantly may decrease MOTRIN blood levels.
Coumarin: bleeding has been reported in patients taking MOTRIN and coumarin.
Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal, of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.
Incidence Greater Than 1% (but less than 3%)—Probable Causal Relationship
Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).
Incidence Less Than 1%—Probable Causal Relationship**
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence Less Than 1%—Causal Relationship Unknown**
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis, cataracts; **Hematologic:** Bleeding episodes (eg, epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction, acidosis; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **Renal:** Renal papillary necrosis.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Do not exceed 3200 mg/day.
Rheumatoid arthritis and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
How Supplied:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
Bottles of 500	Bottles of 500	Bottles of 100
Unit-dose package of 100	Unit-dose package of 100	Bottles of 500
Unit of Use bottles of 100	Unit of Use bottles of 100	

Caution: Federal law prohibits dispensing without prescription. *For additional product information, see your Upjohn representative or consult the package insert.*
*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
MED B-8-S
June 1985
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CONTINUING MEDICAL EDUCATION

(Continued from Page 319)

PEDIATRICS

October 2-3—**42nd Annual Brenneman Memorial Lectures.** American Academy of Pediatrics at Los Angeles. Wednesday-Thursday. 13 hrs. $185. Contact: Eve Black, PO Box 2022, Inglewood, CA 90305.

October 11-12—**The Treatment of Childhood Trauma and Bereavement.** Mental Research Institute at Palo Alto. Friday-Saturday. 8 hrs. Fee: $100. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 11-12—**27th Kaiser-Permanente Pediatric Symposium.** Southern California Permanente at Town and Country Hotel, San Diego. Friday-Saturday. Contact: Lilia M. Guerrero, Dept. of Clinical Services, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 25-27—**Current Advances in Pediatrics.** UC at Irvine at Disneyland Hotel, Anaheim. Friday-Sunday. 13.5 hrs. Contact: Sharon Richard, Program Coordinator, Continuing Medical Education, Memorial Medical Center, UC Irvine.

October 26-November 2—**10th Annual Pediatrics for the Practitioner.** Memorial Medical Center at Mauna Kea Beach Hotel, HI. Saturday-Saturday. 20 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

November 8-11—**7th Annual Las Vegas Seminars/ Pediatric Update.** American Academy of Pediatrics at Inglewood. Friday-Monday. Fee: $250. Contact: American Academy of Pediatrics Chapter 2, PO Box 2134, Inglewood 90305.

November 22-25—**Clinical Pediatrics.** American Academy of Pediatrics at Las Vegas. Friday-Monday. Contact: Eve Black, Exec. Sec., PO Box 2134, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

October 10-12—**American Academy of Clinical Psychiatrists.** Department of Psychiatry, Ohio State University at Meridien, San Francisco. Thursday-Saturday. 13 hrs. Fee: No Charge. Contact: Henry A. Nasrallah, Professor and Chairman M.D. Department of Psychiatry, Ohio State University.

October 18-20—**Mind of a Murder.** Southern California Psychiatric Society at Hotel Del Coronado, San Diego. Friday-Sunday. 9 hrs. $95. Contact: Sharon Karp, 2001 S. Barrington Ave., #214, Los Angeles, CA 90025. (213) 477-1041.

(Continued on Page 412)

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★ **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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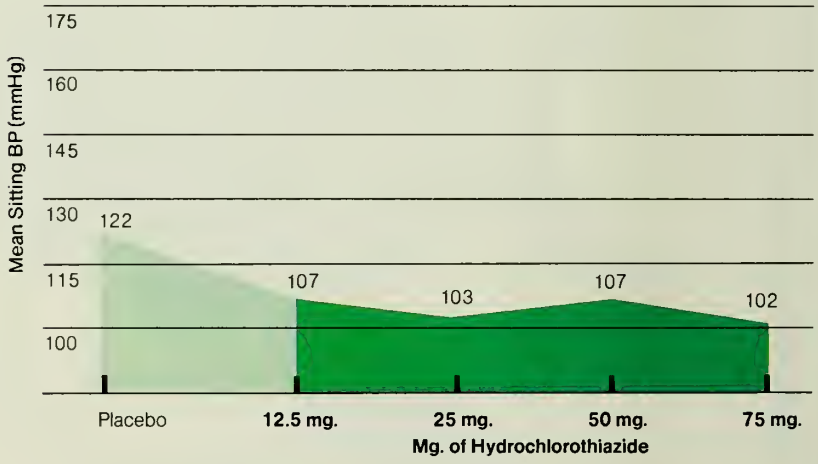

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The Effects of Magnetic Resonance Imaging on Intravenous Infusion Devices

MARY B. ENGLER, MS, *and* MARGUERITE M. ENGLER, MS, *Bethesda, Maryland*

We evaluated the effects of magnetic resonance imaging on the accuracy of three types of intravenous infusion pump devices, IVAC 530, IMED 927 and IMED 960/965. The devices were exposed to a 2,800-gauss static magnetic field at a pulsed radio frequency of 11.9 MHz operating at a maximum power of 1,200 W. Each device was tested at low, medium and fast flow rates in a controlled environment and during magnetic resonance imaging. Intravenous therapy could be carried out normally during magnetic resonance diagnostic imaging only with the IVAC 530 infusion device.

(Engler MB, Engler MM: The effects of magnetic resonance imaging on intravenous infusion devices [Clinical Investigation]. West J Med 1985 Sep; 143:329-332)

The clinical importance of magnetic resonance (MR) imaging in patient diagnosis is becoming widely recognized. Mechanical functions can be affected significantly by exposure to MR imaging, however, creating special safety considerations for patients using any instrumentation during such studies. The safety of intravenous infusion devices is always of significant concern, but the possible effect of MR imaging on these devices requires particular consideration.

Precise intravenous fluid or medication delivery can be critical to a patient. The potential for fluid overload, dehydration, medication bolus or nontherapeutic medication delivery can be life-threatening, especially to a critically ill patient. In this study, we investigated the possibility that magnetic field interaction with intravenous devices might result in inaccurate fluid delivery to a patient. This was undertaken by examining the effects of the magnetic field of MR imaging on the function of three types of intravenous devices—the IMED 927 volumetric pump, the IMED 960/965 volumetric pump and the IVAC 530 nonvolumetric peristaltic pump.

Review of Literature

MR imaging is a valuable diagnostic technique. The concept of MR spectroscopy was developed in 1946 by Bloch and by Purcell and co-workers,[1,2] and has been used for years in analytical chemistry and biology. Damadian used the MR method in 1971 for detecting cancer in human tissue.[3] The first MR imaging study was done in the early 1970s by Lauterbur, who obtained cross-sectional pictures of water-filled capillary tubes.[4] In 1977 the first human body MR images were made[5] and further perfected with improved images of the extremities and head.[6,7]

The images displayed by MR imaging are similar to x-ray computed tomographic (CT) scans, but MR imaging is superior to computed tomography in some regards. CT scans require exposing patients to potentially harmful ionizing irradiation, whereas MR imaging uses pulsed and static magnetic fields at levels not known to cause any harm to the human body. MR imaging also gives good discrimination of the body's soft tissues, whereas CT shows only density.

Magnetic resonance imaging has shown promise for evaluating myocardial function and for detecting atherosclerosis, cancer, brain and demyelinating diseases and kidney, liver and pancreatic diseases.[8-11] Future physiologic applications are also predicted for MR imaging to provide essential biochemical and metabolic information.[12-14]

As with any new procedure, there are potential problems with MR imaging. It was originally postulated that MR imaging units could induce electrical currents, resulting in local tissue heating with metal surgical clips and prostheses. No significant heating of clips or prostheses has been reported as yet.[15] Patients with cardiac pacemakers should not have MR imaging. A pacemaker might be reprogrammed or switched into a fixed-rate mode by the magnetic field in a manner similar to pacemaker magnets used clinically to change modes. Pacemaker interference and a torque movement sufficient to cause rotation have been documented with exposure to magnetic resonance.[16] This torque movement resembles the dial of a compass moving in the direction of the magnetic

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Reprint requests to Mary B. Engler, MS, National Institutes of Health, Building 10, Room 7D50, Bethesda, MD 20205.

ABBREVIATIONS USED IN TEXT

CT = computed tomographic
df = degrees of freedom
MR = magnetic resonance

field. Possible rotation of the pacemaker within the surgically implanted area is cause for concern, as is the potential for inducing arrhythmia by conduction generated in the pacemaker cardiac lead. These pacemaker problems appear to be associated with ferromagnetic metal components.

Other research has indicated that MR imaging may generate enough longitudinal forces and torques to risk dislodgement of certain vascular clips, resulting in hemorrhage or injury to surrounding tissues.*[17] Clearly, all of the reported effects of MR imaging are of paramount clinical importance; at present, no reports appear in the literature on the effects of MR imaging on intravenous infusion devices.

Methods

Three types of intravenous devices that regulate intravenous infusion were tested. The total study sample included six IMED 927 volumetric pumps, three IMED 960/965 volumetric pumps and four IVAC 530 nonvolumetric peristaltic pumps. As a control, the intravenous devices were first tested in the ambient earth's magnetic field.† Then each device was subjected to the same tests in varying magnetic field strengths near the MR system's magnet.

Each intravenous pump device was evaluated at slow, medium and fast rates in a controlled environment and within the fringe magnetic field of the MR system. The devices were exposed to a 2,800-G static magnetic field with a pulsed radio frequency of 11.9 MHz operating at a maximum power of 1,200 W. The magnetic field at the center of the MR imaging magnet opening was measured at 1,500 G. The MR imaging magnetic fringe field strengths at each of the intravenous device locations were measured with a Digital Gaussmeter Model 811 (F. W. Bell, Inc).

The study was conducted using 0.9% sodium chloride solution infused through manufacturer's infusion sets specific for each type of pump. The solution was allowed to flow through the tubing, connected to plastic syringes for the slow and medium rates and graduated cylinders for the fast rate. Single-use plastic syringe (12 ml, 60 ml) fluid collections serve as a method of measuring delivered volume equivalent to using graduated cylinders. All air was expelled from the tubing and syringes to ensure accuracy before testing. The effluent from each device at the three rates was collected and measured at one-hour intervals during the control and MR imaging trials. All devices operated on line current rather than batteries during both control and magnetic exposure.

The intravenous devices in the system's magnetic fringe field were placed at two locations away from the center of the MR unit opening (Figures 1 and 2). Close positioning of the intravenous devices was measured at 0.9 m (3 ft), 30 degrees away from the center of the magnet opening. Distant positioning was designated at 4 m (13 ft), 60 degrees away from the center of the magnet opening.

The magnetic fringe field strength of the MR imager for the four IVAC 530 devices at the close position was measured at 415 to 500 G, depending on the vertical location of the device on the intravenous pole. This position for the pole was chosen because it represented the closest practical location during MR imaging. The three IMED 960/965 devices had an MR imaging exposure field of 440 to 525 G at the close location, which was then decreased to the distant position of 9 to 10 G. The six IMED 927 devices were exposed to a close MR imaging field of 450 to 700 G, which was decreased to 9 to 12 G at the distant location.

Uniform gauss values in the MR imaging fringe field were difficult to maintain due to the logistics of device placement. Biomedical engineering performance checks of the devices were conducted before and after the study to certify electrical circuitry performance and conformance with the manufacturers' specifications. Statistical significance of differences was assessed by paired Student's *t* test. The *t* test was used to determine the effect of the MR imaging exposure on device accuracy. The effects of confounding variables—that is, device type and infusion speed—were determined by two-factor analysis of variance. A two-sided *P* value of less than .05 was considered statistically significant.

Results

All of the IMED 927 and IMED 960/965 intravenous devices tested were within the manufacturer's specifications ±2% accuracy before MR imaging exposure. However, the IVAC 530 devices were ±3.3%, which exceeds the manufacturer's prescribed accuracy for a controlled environment. Because this difference in calibration for the IVAC 530s was known before measurement in the magnetic field, it was taken into account when reporting deviations in accuracy due to magnetic effects.

The IMED 927 devices *failed* to deliver fluid in the 450 to

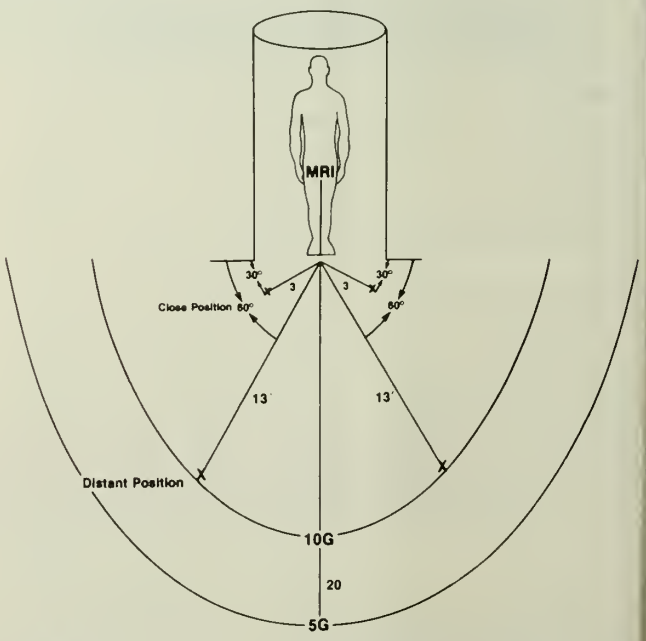

Figure 1.—The magnetic strength field plot of magnetic resonance imaging (MRI) and intravenous device positions. G = gauss

*It should also be emphasized that safety precautions must be undertaken with any ferromagnetic object including intravenous devices in the MR imaging vicinity. Ferromagnetic objects can be converted into dangerous projectiles within the MR imaging field, posing considerable risk to a patient, personnel, or both.

†Gauss (G) is a unit of magnetic field strength. The earth's magnetic field is approximately 0.5 G.

700 G MR imaging close fringe field; thus, no statistical analysis was completed on these data. The IMED 960/965 devices were significantly affected by 440 to 525 G exposure ($t = -2.695$, degrees of freedom *[df]* 8, $P = .02$). Although the mean error was only 1.5% (less than the error allowed by the manufacturer's specifications), the range across the three samples tested was from 1% to 4%. The IVAC 530 devices operated normally at the calibration level within the 415 to 500 G close magnetic field with no statistically significant difference detected between the flow rates in the control and the magnetic environment ($t = 0.165$, df 11, no significance).

In an effort to identify a location in the MR imaging fringe field that would allow for proper operation of both types of IMEDs, the magnetic field exposure was decreased until proper operation was observed at 9 to 12 G for the IMED 927 and 9 to 10 G for the IMED 960/965. This gauss level was measured at the distant position, as previously described. There was no significant difference between flow rates for the IMED 960/965 in the control and decreased MR imaging field exposure ($t = -0.255$, df 8, no significance). The MR imaging exposure for the IMED 927 was decreased to 9 G for three devices, 10 G for two devices and 12 G for one device. A statistically significant difference in flow rate persisted in the 10 to 12 G range ($t = -3.306$, df 8, $P < .01$); the mean error rate was 2.3% (above the manufacturer's ±2% specification for accuracy). The data from the three IMED 927 devices at 9 G also reflected a persistence in statistically significant flow rates ($t = -8.044$, df 8, $P < .005$), although the mean error rate was only 1.3%. It is interesting to note that the error rates for the IMED 927 decrease as the MR imaging field exposure decreases: 12 G, 2.7%; 10 G, 2.0%, and 9 G, 1.3%.

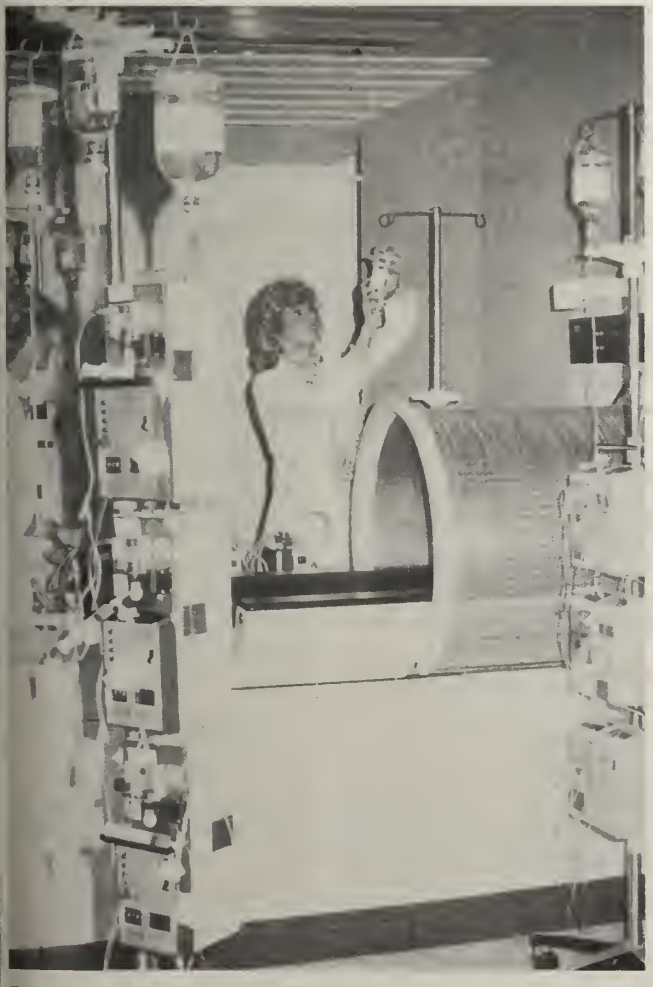

Figure 2.—Intravenous infusion pump devices within the magnetic resonance imaging area during testing. (Photo courtesy of the National Institutes of Health, Bethesda, Maryland).

Differences in the operation of the two types of IMEDs in the decreased MR imaging field were then compared using analysis of variance techniques. Three devices of each type were matched for MR imaging exposure (one device at 9 G, two devices at 10 G) only at the medium flow rate to ensure device independence. There were no statistically significant differences between the IMED 927 and 960/965 devices when the MR imaging field was decreased. There was, as expected, a statistically significant difference between the operation of the IVAC 530 and IMED 960/965 in the original MR imaging field ($t = -26.51$, df 5, $P < .0001$).

Biomedical engineering checks of all intravenous devices certified proper manufacturers' performance specifications (excluding the IVAC 530 devices calibrated at ±3.3% accuracy) and electrical circuitry following MR imaging exposure.

Discussion

The data verify that the IVAC 530 can operate normally within the MR imaging field. The IMED 960/965 can also function properly, but at a decreased MR imaging field of 9 to 10 G. The IMED 927 did not operate optimally at the decreased MR imaging field of 9 to 12 G; the mean error rate was 0.3% above the manufacturer's ±2% specifications for accuracy.

A significant difference exists between the IMED 927 in the controlled environment and the 450 to 700 G MR imaging field. The IMED 927 devices' complete *failure* to deliver fluid in this field is clinically critical. It is apparent that the IMED 927 device cannot be used for intravenous infusion regulation in close proximity to an MR imaging unit. Although the mean error for the IMED 960/965 in the 440 to 525 G MR imaging field was within the manufacturer's ±2% specification for accuracy, the range of errors was from 1% to 4%. This large rate of error could jeopardize patient safety. Furthermore, the IMED 960/965 and 927 devices at the decreased magnetic field strength showed no statistically significant difference between their accuracies, implying the monitoring of these devices at 9 to 12 G is warranted.

If the use of the IMED 960/965 at a distant location in the MR imaging field is considered, the feasibility of additional intravenous tubing attached from the patient to the IMED should be further addressed. Additional tube length appears to be necessary to limit access with the IMED 960/965 to about 10 G.

A limitation of the study is that while the measurements were made under conditions simulating clinical use, they were in fact not done under actual patient use. Possible confounding variables such as device age, frequency of device use and different viscosity of intravenous fluids were not in the scope of this study.

Clinical implications include a clinician's judgment in selecting an intravenous pump device to assure proper delivery of fluid or medication to a patient during MR imaging. The

data support the safe use of the IVAC 530 close within the MR imaging field and the IMED 960/965 at a level of 10 G. The IMED 927 and 960/965 should not be used close within the MR imaging field. Studies of the effect of MR imaging on additional types of intravenous devices, and the potential for intravenous devices to cause artifacts on MR images, should be pursued.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Laser Therapy for Plantar Warts

QUESTION:

Is it accepted medical practice to treat plantar warts by laser therapy?

OPINION:

In the opinion of the Scientific Advisory Panels on Dermatology and Orthopedics, laser therapy can be considered established practice in the treatment of plantar warts, but not as a routine or initial form of therapy. Its use should be reserved for lesions that have proved therapeutically unresponsive to other conservative means of treatment such as chemocautery, cryosurgery or electrosurgery. Where lesions are recurrent or very extensive, such as mosaic warts, or multiple, particularly periungual warts, laser therapy may be justified. For most patients with plantar warts, however, there is no conclusive evidence that laser therapy is more effective than less expensive modalities.

Effects of Accidental Chlorine Inhalation on Pulmonary Function

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In an industrial accident, 19 previously healthy workers were briefly exposed to high concentrations of chlorine gas. Pulmonary function tests were done at intervals for about two years but complete follow-up data were available in only 11 subjects. Immediately following the exposure, airway obstruction was detected in 10 of 19 patients; 700 days later this was found in only 3 of 11 patients. Two of these three patients had a history of smoking, however. The mean residual volume was 141% ± 97 (mean ± standard error of the mean) on day 1. In subsequent follow-up studies, the residual volume progressively fell in all patients, and 700 days later the mean residual volume was 90% ± 5. In 5 of the 19 subjects, all pulmonary function test results were within normal limits on day 1. Apparently in some subjects acute exposure to chlorine gas may cause immediate changes in the lung functions, but these changes gradually resolve. Because of the small number of patients in our series, however, the long-term effects of chlorine are less apparent.

(Charan NB, Lakshminarayan S, Myers GC, et al: Effects of accidental chlorine inhalation on pulmonary function [Clinical Investigation]. West J Med 1985 Sep; 143:333-336)

Chlorine is a heavy, yellowish green irritant gas with a specific gravity 2.49 times that of air. It is commonly used as a bleaching agent in the paper and textile industries and also to disinfect water and sewage. For industrial uses, it is liquefied under pressure and stored or transported in steel cylinders. When released, 1 liter of liquid chlorine produces 434 liters of chlorine gas at 25°C.[1] Lung injuries from inhalation are usually a consequence of accidental leakage from the containers and result primarily from the oxidative effect of nascent oxygen liberated by chlorine gas in the presence of water. The formation of hydrochloric acid causes further damage, although it is 20 times less severe than the oxidative effect of chlorine.[2]

The reported consequences of accidental chlorine inhalation have been conflicting with residual pulmonary abnormalities noted in some series,[3] whereas in others no significant permanent damage was found.[4,5] This report deals with an industrial accident in which 19 healthy subjects were exposed to high concentrations of chlorine. We report the immediate and long-term effects of chlorine exposure on the pulmonary function of these subjects.

Exposure Incident and Methods

The accident occurred in a pulp mill. A flexible hose connecting a railroad car filled with liquid chlorine accidentally became disconnected, resulting in the escape of a large volume of chlorine gas.

The ambient temperature at that time was about −1°C (30°F) without an appreciable wind. Because the walls of adjoining buildings were warm, the chlorine gas rose along the walls and settled as a yellow-green cloud on the roof. The actual concentration of chlorine in this cloud was not measured but was estimated to be more than 1,000 parts per million (ppm) in view of the color of the cloud. Several construction workers were on the roof of this building with no prior experience with chlorine gas and they did not have gas masks. When they saw the green cloud coming up, they tried to escape into a chlorine-free area inside the building. They were all exposed to the chlorine, however, although the duration of exposure varied in individual subjects from a few seconds to a few minutes. There were no deaths.

All 19 patients were men with a mean age of 37 years (range, 25 to 61 years); 14 were current smokers, 3 were

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ABBREVIATIONS USED IN TEXT

DLCO = diffusing capacity of the lung for carbon monoxide
FEF_{25-75} = mean forced expiratory flow during 75% to 25% of vital capacity
FEV_1 = forced expiratory volume in one second
SD = standard deviation
SEM = standard error of the mean
VC = vital capacity

exsmokers and 2 had never smoked. Pulmonary function test results before the exposure were not available for any of them. All exposed workers were admitted to hospital for 24 to 48 hours and most of them were given supplemental oxygen. Corticosteroids were not given. The initial evaluation included physical examination, chest roentgenogram and arterial blood gas determinations. Pulmonary function tests were done on all subjects within the first 24 hours. The pulmonary function tests included spirometry, static lung volumes by the nitrogen wash-out method and single-breath diffusing capacity of the lung for carbon monoxide (DLCO). The predicted normal values used were those of Higgins and Keller for spirometry,[6] Goldman and Becklake for lung volumes[7] and McGrath and Thomson for the DLCO.[8] These pulmonary function tests were repeated after 10 days in all, after 40 days in 16, after 310 days in 13 and after 700 days in 11 workers.

Results

The immediate symptoms of exposure included irritation of eyes, nose and throat, tightness in the chest and paroxysms of cough. The symptoms subsided within 24 to 48 hours in all patients. On physical examination there were no abnormalities and chest roentgenograms on admission showed transient pulmonary infiltrates in five patients that cleared in follow-up studies. Clinically unmistakable pulmonary edema did not occur in any patient.

Immediately following the exposure, 10 of 19 patients (53%) had a ratio of forced expiratory volume in one second (FEV_1) to vital capacity (VC) of less than 75%, suggesting airflow obstruction (Table 1), and, of these, 6 showed partial reversibility (improvement in FEV_1 of greater than 15%) after inhaling isoproterenol. After ten days, this ratio was less than 75% in only seven (37%) patients. The airflow obstruction, as indicated by the FEV_1-VC ratio and a mean forced expiratory flow during 75% to 25% of vital capacity (FEF_{25-75}) below 60% of predicted, continued to abate in some subjects, and two years later only 3 of 11 subjects studied had an FEV_1-VC ratio of less than 75%. One of these three persons had never smoked.

Of the 19 patients, 13 (68%) had a residual volume of greater than 120% of predicted immediately following the exposure (Figure 1 and Table 1). However, the residual volume progressively fell in subsequent studies, and two years later 6 of 11 patients (55%) had residual volumes of less than 80% of predicted. The absolute fall in residual volume in these six patients was 0.58 ± 0.19 liters (mean ± standard deviation [SD]) between day 10 and day 700. None of the 11 subjects studied on day 700 had a residual volume of more than 120% predicted. The mean residual volumes on day 1, day 7, day 40, day 310 and day 700 were $141\% \pm 9$ (mean ± standard error of the mean [SEM]), $121\% \pm 6$, $106\% \pm 6$, $97\% \pm 7$ and $90\% \pm 5$, respectively. There was a significant difference between mean residual volume (% predicted) on day 1 and day 700 ($P < .001$) and also between day 40 and day 700 ($P < .05$). Similar reductions, although of lesser degree, were noted in functional residual capacity. No significant changes were noted in total lung capacity, functional residual capacity and vital capacity (Figures 1 and 2).

Although not all 19 subjects completed follow-up pulmonary function testing at two years, a telephone contact with these patients found that none of the subjects had died and, for the most part, they were asymptomatic.

Single-breath nitrogen plateau (phase III) and closing volume (phase IV) were also studied. However, the number

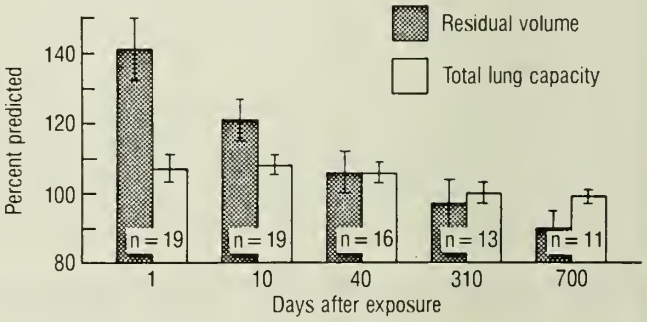

Figure 1.—Serial changes in residual volume and total lung capacity following chlorine exposure (mean ± standard error of the mean). n = number of patients studied

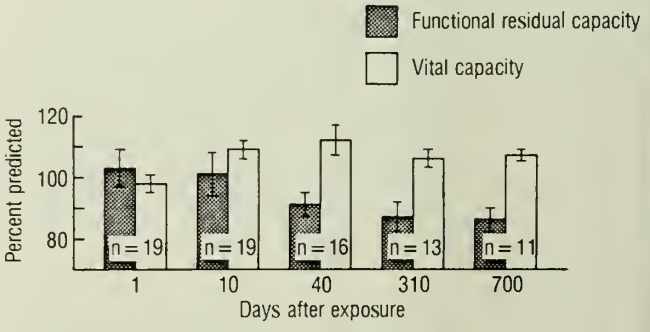

Figure 2.—Serial changes in functional residual capacity and vital capacity following chlorine exposure (mean ± standard error of the mean). n = Number of patients studied

TABLE 1.—*Sequential Pulmonary Function Tests*

	Day 1 *N = 19 (%)*	*Day 10* *N = 19 (%)*	*Day 40* *N = 16 (%)*	*Day 310* *N = 13 (%)*	*Day 700* *N = 11 (%)*
FEV_1-VC ratio below 75%	10 (53)	7 (37)	6 (38)	5 (38)	3 (27)
RV above 120% of predicted ..	13 (68)	7 (37)	3 (19)	2 (15)	0
RV below 80% of predicted ...	0	0	1 (6)	4 (31)	6 (55)

FEV_1 = forced expiratory volume in one second, VC = vital capacity, RV = residual volume

of patients with abnormal results was no greater than the number of patients with an abnormal FEV_1-VC ratio or abnormal FEF_{25-75}. Arterial blood gas determinations were made in all the subjects, and on day 1, two were found to have mild hypoxemia that improved to normal by day 10. Single-breath DLCO studies did not show any consistent trends or abnormalities.

Discussion

The earliest accurate account of chlorine inhalation associated with lung injury was reported by Lehmann in 1887,[9] who described hemorrhagic pulmonary edema in animals following experimental exposure to chlorine gas at a concentration of 1 ppm. However, it was not until the second year of World War I when chlorine gas was introduced as a weapon of war that its toxic potential received any particular attention. The pulmonary effects of chlorine on about 2,000 victims of gas attacks were reported by Berghoff.[10] He found that in 50% of the soldiers either bronchitis or emphysema developed and that the subjective symptoms far exceeded clinical findings.

The long-term pulmonary sequelae of accidental exposure to chlorine in humans have been described in few reports. However, the degree and the type of abnormality vary from report to report. Kowitz and co-workers[3] studied 11 subjects serially for three years and reported decreased lung volumes, presumably due to patchy atelectasis and nodular scarring. They postulated that humans who inhale a high concentration of chlorine gas suffer acute alveolar damage that heals with subsequent pulmonary fibrosis in six months to two years. However, none of their patients had a lung biopsy. Weil and associates[4] studied 12 persons serially for seven years following accidental chlorine exposure. They concluded that significant permanent lung damage does not result from acute exposure to chlorine gas. Review of their data, however, showed that in 1964 none of the four subjects studied had residual volumes of less than 80% of predicted, whereas in 1968 five of seven had a residual volume below 80% of predicted. Chester and colleagues[11] studied the effects of long-term exposure to low concentrations of chlorine (average concentration, 1 ppm) in chlorine gas plant workers. Of the 139 workers, 55 had additional accidental exposures severe enough to require oxygen therapy. They found only three workers with abnormalities, and they had evidence of significant airway obstruction.

Winternitz and co-workers[12] exposed dogs to massive concentrations of chlorine gas to study the sequential morphologic changes. They found that animals dying within 24 hours of exposure had tracheitis, bronchitis with peribronchial inflammation and focal necrosis of lungs. The animals dying two to five days after the exposure had evidence of pulmonary infection, mainly pneumonia and bronchitis, whereas the animals dying 15 to 193 days after the exposure showed evidence of bronchitis and bronchiolitis. The small airway disease was seen only in the acute phase and most of the animals recovered completely from this, suggesting that the involvement of the small airways was mild and did not result in the severe bronchiolitis obliterans usually seen with massive and prolonged exposure.

The airflow obstruction that was noted in our subjects on day 1 could be attributed to acute inflammatory changes in the airways. On days 310 and 700, 5 of 13 (38%) and 3 of 11 (27%) patients continued to show spirometric evidence of airflow obstruction. Of the three patients who continued to have airflow limitation, two were heavy smokers, and in these two patients airflow limitation could be related to their smoking habits. Only one person was a nonsmoker and chlorine could have been the causative agent in him. However, because of the small number of patients with this abnormality in this series, no conclusion regarding the long-term effects of chlorine inhalation on airflow obstruction can be drawn from this study.

An elevation of the residual volume immediately following chlorine exposure could be explained by air trapping as a result of bronchospasm and mucosal inflammation of the airways. Therefore, the residual volume would be expected to fall rapidly to the baseline values with the resolution of mucosal inflammation and edema. This would explain the decrease in the residual volume in the first ten days. A further fall in the residual volume from day 10 to day 700 also appears to be related to continuation of the healing process. Although on day 700, the mean residual volume in our study was within normal limits, 6 of the 11 subjects had a residual volume below 80% of that predicted. The cause for a decreased residual volume in these subjects is not apparent. Mild peribronchiolar fibrosis in the healing phase would make the bronchioles stiffer and hence more resistant to closure during exhalation. Leith and Mead[13] have shown that the residual volume in healthy, young persons (younger than 35 years) is determined by the limitation of chest wall, and in older persons (older than 35 years) it is determined by airway collapse. Stiffening of the airways by peribronchial fibrosis would keep the airway patent at lower lung volumes, thus allowing a low residual volume. Another possibility is that the pulmonary injury heals with fibrosis, which would increase elastic recoil of the lung. The increased elastic recoil will also favor a low residual volume by its tethering effect on small airways, tending to keep them open at low lung volumes while permitting a nearly normal expansion at total lung capacity. Without a lung biopsy specimen in these subjects, the mechanisms described above remain speculative. The clinical implications of this degree of reduction in the residual volume seen in our patients are not apparent and it is unlikely that it would cause any major respiratory symptoms.

Currently, chlorine is used extensively in industry, and the National Institute of Occupational Safety and Health has estimated that 15,000 workers in the United States are at risk for possible exposure to chlorine.[14] Pulmonary injuries due to inhaling chlorine are usually a consequence of industrial accidents. Therefore, the concentration and the duration of exposure vary in the individual subjects. Furthermore, chlorine is a strong respiratory irritant, which tends to limit the length of exposure. This could explain why some studies show no residual pulmonary function abnormalities. However, a longer duration of exposure to higher concentrations of chlorine gas may result in long-term pulmonary function abnormalities.

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Medical Practice Question

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Stereotactic Heavy-Ion Irradiation of Arteriovenous Malformations

QUESTION:

Is it accepted medical practice to treat arteriovenous malformations by the radiosurgical method of stereotactic heavy-ion irradiation?

OPINION:

In the opinion of the Scientific Advisory Panels on Neurosurgery and Radiology, stereotactic heavy-ion bragg peak radiosurgery is considered a promising but still investigational treatment for deep, inoperable arteriovenous malformations (AVMs) of the brain. The procedure has been advocated for those select patients in whom the AVM cannot be safely surgically excised, cannot be treated with any form of embolization or in which, following embolization carried out at one or multiple stages, there remains some residual AVM that cannot be controlled. To date, only two centers in the United States have the specially trained personnel and sophisticated equipment necessary to apply this treatment method.

Though recent reports indicate that this technique can be applied safely, effectively and at low risk to patients, the total number of patients treated thus far has been small. Follow-up in two of the three studies reported has been for a relatively short period of time, two years or less. In one series, only 20% of patients had complete obliteration of the AVM; in the other, although most patients had a decrease in the size of the AVM after a period of months, none had complete obliteration.

Long-term study findings are not yet available to address questions such as recanalization, delayed hemorrhage, the delayed response in the reduction and obliteration of the AVM and the associated risks of large dose radiation. Therefore, as neither the technique nor its outcome has been conclusively defined and because continued basic research and clinical investigation is advocated by those working in this field, stereotactic heavy-ion bragg peak radiosurgery for arteriovenous malformation should be classified as an investigational procedure.

Toxic Shock Syndrome in Utah—1976 to 1983

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The sustained high incidence of staphylococcal toxic shock syndrome (TSS) in Utah provided an opportunity to examine changes in the epidemiology of this disease during a period of greater media attention to the syndrome and increased scientific understanding of its etiology and pathogenesis. An apparent peak in the statewide incidence of TSS in 1980 appears in part attributable to self-reporting of outpatient cases. The incidence of the syndrome in patients having a nasal operation appears equal to or greater than the incidence in menstrual-age women. The case-fatality ratio and recurrence rate of TSS have declined since widespread recognition of the syndrome, possibly related to earlier diagnosis and initiation of antistaphylococcal therapy. Identifying milder cases has also contributed to a lower mortality.

(Jacobson JA, Nichols CR, Kasworm EM: Toxic shock syndrome in Utah—1976 to 1983. West J Med 1985 Sep; 143:337-341)

Although Todd and co-workers first labeled toxic shock syndrome (TSS) in 1978,[1] most of the medical profession and the public first learned of it from the lay press in 1980. TSS was subsequently characterized as a new, dangerous, often lethal illness strongly associated with menstruation, tampon use and possibly the use of one brand of tampon in particular.

Older reports of "staphylococcal" scarlet fever,[2] Todd's investigation of toxic shock syndrome in children[1] and case-control studies conducted in 1980[3,4] all implicated *Staphylococcus aureus* in the pathogenesis of TSS. Strains of *S aureus* recovered from patients with TSS have been associated with the production of exotoxins: specifically, epidermal toxin,[5] staphylococcal enterotoxin F[6] and staphylococcal pyrogenic exotoxin C.[7] The latter two may represent the same material in different laboratories. The pathogenic role of these toxins in humans is not yet well established, and tests for identifying their presence are not widely available. Thus, the diagnosis of TSS continues to be a clinical one and requires meeting criteria established in a case definition.

While there remains some debate as to whether staphylococcal toxic shock syndrome is a "new" disease, there is little doubt that it has been more commonly recognized in recent years. The incidence of the syndrome reported nationally has peaked and fallen within the past five years,[8] and this has been attributed to changes in recognition and reporting, in the availability of certain catamenial products and possibly in the way in which tampons are used. Accompanying the change in reported incidence of this syndrome has been an appreciation of a wider variation in clinical expression and the realization that the syndrome can and often does occur independent of menstruation.[9]

The incidence of reported cases of TSS in Utah and several other states has been inexplicably high and sustained. Utah was one of only four states in 1980 with an incidence above 1 per 100,000. The others were Minnesota, Wisconsin and Oregon.[10] As of June 1983, three states—Utah, Wisconsin and Minnesota—accounted for 28% of TSS cases reported in the United States.[8]

The first 135 cases of TSS reported in Utah had onsets of illness from 1976 to 1983. These cases provided an opportunity to examine secular trends and changes in the epidemiology, clinical presentation, management and outcome of this syndrome during the period when knowledge about and awareness of TSS were increasing rapidly.

Patients and Methods

The toxic shock syndrome has been a reportable disease in Utah since March 1980, when Utah physicians were alerted about this syndrome by an article in the *Communicable Disease Newsletter* published by the Utah Department of Health. Cases suggestive of TSS have been identified through reporting by physicians, hospitals, bacteriology laboratories, patients, patients' family members and local health departments. Reports have also been solicited by active monthly telephone surveillance of infection control practitioners in all 38 hospitals in the state. The state health department has sought details of the illness from the patients' physicians, the

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medical records and in most instances the patients. A case is considered confirmed if it meets the modified case definition used by the Centers for Disease Control.[10] For the purpose of this study, additional case-finding efforts included a search of the consultation records of a hospital-based infectious disease division and a telephone survey of all of the otorhinolaryngologists practicing in the state. The state of Utah records demographic and clinical information about cases of the toxic shock syndrome on a form designed for that purpose. These records and the medical records of patients admitted to LDS Hospital were the primary sources of data for this report. The LDS Hospital is a 530-bed community and tertiary care hospital academically affiliated with the University of Utah Medical School. There are two full-time infectious disease physicians on the hospital staff. An infectious disease fellow and internal medicine trainees are regularly assigned to the clinical consultation service. Frequent formal and informal teaching sessions about TSS have been conducted at this hospital since 1980.

Cases were defined as menstrual if their symptoms of TSS began during or within two days of menses. Cases were considered postpartum if they occurred after delivery but more than two days before menses resumed. Postsurgical cases were those in which there was an obvious temporal and anatomic relation to an operative procedure independent of menstruation. All other cases were categorized as spontaneous. A recurrent case of TSS was defined by the presence of desquamation and at least two major criteria of the case definition.[3]

Population data were derived from the 1980 census and official estimates of the population for the years 1976 to 1983. Data on live births were derived from the Utah Bureau of Vital Statistics.

The relative risk for a menstrual-age woman was calculated by dividing the incidence of TSS in this population by the incidence in men and nonmenstrual-age women. The percentage of risk attributable to being a menstrual-age woman was calculated by subtracting the incidence in the population exclusive of this group from the incidence in this group and dividing by the incidence in menstrual-age women. The relative risk of menstruation was calculated in a similar fashion using the assumption that about 30% of menstrual-age women would be menstruating or would be within two days of menses on the day a case occurred. Thus, the relative risk of menstruation for menstrual-age women was the incidence in menstruating women divided by the incidence in nonmenstruating women of menstrual age. The percent attributable risk was the difference in those rates divided by the incidence in menstruating women.

Results

The first reported case of TSS in Utah occurred in 1976. Between 1976 and July 1983, 134 more cases had occurred and been reported. The incidence peaked in 1980, a year of intense publicity about the association between the syndrome and menstruation and tampon use (Figure 1). Subsequently, the overall incidence has been about 1.7 per 100,000 persons per year. There has been no consistent seasonal trend. Most of the sharp increase in incidence in 1980 could be accounted for by menstrual cases occurring at a rate of 12.7 per 100,000 menstrual-age women and averaging 5.3 since then. The incidence of nonmenstrual cases has been relatively constant since 1977, averaging about 0.13 per 100,000 per year. All but one case that occurred before 1979 were menstrual, while in 1980 to 1983, three to five cases per year (9% to 33% of the total) have been unrelated to menstruation (Figure 2). Of 120 menstrual cases, 119 have occurred in women using tampons. The relative risk for women of menstrual age (15 to 44 years) has declined from a high but indeterminate value to a range of about 20 to 30 since 1980. The attributable risk percent for this group has ranged from 95% to 100%. In years when it could be determined, the relative risk of menstruation in women of menstrual age was sharply higher in 1980 at 168, and the average for the period since has been 58. The attributable risk percent for menstruation, however, in menstruating women has consistently been between 92% and 100%. Obviously, most cases of TSS occur in women, but when menstrual and postpartum cases are excluded, the female-male ratio is still 4.5 to 1. Cases were not identified in men before 1981. All cases of TSS in Utah have occurred in whites. The black population, however, is only 0.63% of Utah's population and numbered 9,225 in the 1980 census.

The average age of the women in menstrual cases of TSS is 24.3 years. The age-specific attack rates by five-year age

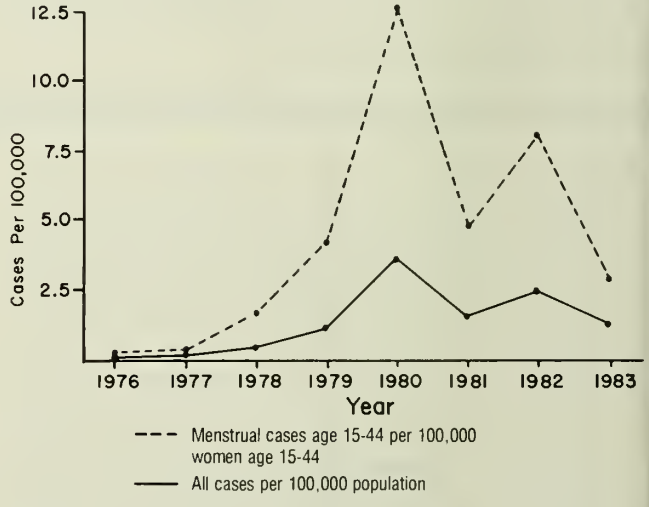

Figure 1.—Incidence of toxic shock syndrome in Utah, 1976 to 1983.

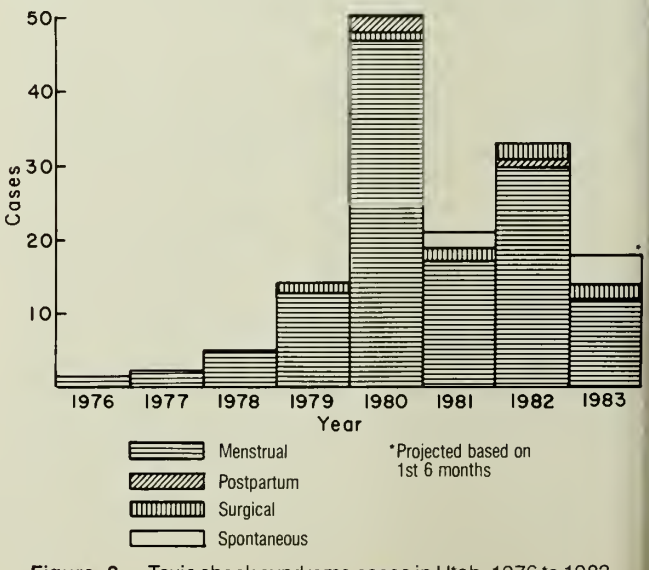

Figure 2.—Toxic shock syndrome cases in Utah, 1976 to 1983.

groups show similar rates in women aged 15 to 30 years, 4.5 per 100,000. The attack rate for women aged 30 years and older drops progressively to 0.7 per 100,000 in women aged 45 to 49 years. The average age of patients with menstrual TSS and the pattern of age-specific attack rates for this form of the syndrome have not changed substantially over the past eight years.

Postsurgical cases have occurred following nasal operations (four cases), abdominal hysterectomy (one case) and umbilical herniorrhaphy (one case). The average age of all postsurgical cases was 28.3 years, and for those having a nasal procedure it was 28.5 years. Appropriate denominators were not available with which to calculate incidence and age- and procedure-specific attack rates for all of these cases. However, our survey of ear, nose and throat physicians indicated that for 1981 and 1982, the estimated annual incidence of TSS following a nasal surgical procedure is 32 per 100,000. The average age of patients having such procedures is between 25 and 35 years, suggesting that the age-specific attack rate in this group may not be disproportionately high.[11]

Postpartum cases of TSS were first recognized in Utah in 1980. Based on live births to Utah residents, the average annual incidence for postpartum TSS would be 3.0 per 100,000. The relative risk for the postpartum state has ranged between 0 and 4.2 through 1983.

Spontaneous cases of TSS were first recognized in Utah in 1977. Since 1976, an average of 0.6 cases per year has been confirmed. These have been associated with minor staphylococcal skin infections and, in one case, staphylococcal superinfection of the vesicles of herpes zoster.[12]

At the LDS Hospital, in contrast to the state, the number of cases of TSS per 10,000 admissions, exclusive of transfers, has remained relatively stable since 1977, varying between 0.4 and 0.8, with the exception of 1980 when the incidence was 1.5. Also, in contrast to the rest of the state, the proportion of nonmenstrual cases initially admitted to LDS Hospital is quite high (Figure 3). This has been true since 1977 (4 of 11 versus 12 of 124, $P = .05$).

In the course of this study, we discovered three confirmed and four suspected cases of TSS admitted to LDS Hospital that had not been previously reported. One confirmed case had occurred in 1977, one in 1978 and one in 1982. Thus, as of July 1983, 13 of 16 (81%) cases of TSS at the LDS Hospital had been officially reported to the state.

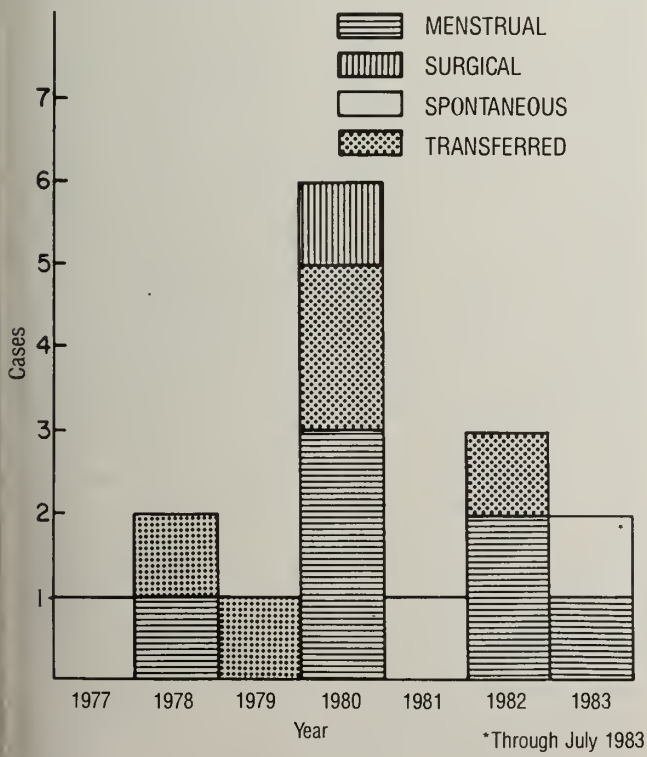

Figure 3.—Toxic shock syndrome cases at LDS Hospital, 1977 to 1983.

Clinical Presentation

The clinical presentation of the 120 menstrual cases of TSS seen in Utah since 1976 conforms closely to published descriptions.[3,4] The only two deaths, however, following menstrual cases occurred before 1980, and these were the only deaths occurring from the syndrome in Utah.

Arthralgias, not specifically mentioned in the case definition, were quite common in patients with menstrual-related TSS (64%) but were not mentioned by other patients. Involvement of the genital mucosa has been regularly reported in cases of menstrual TSS, but it occurred frequently in our nonmenstrual cases as well. Three of four women with surgical and spontaneous cases of TSS had a vaginal discharge described as thick and white.

Management

The severity, complexity and multiple-organ system involvement of TSS is apparent from the diversity of physicians involved in primary or consultative care of the patients (Table 1). Generalists and gynecologists were most likely to see the patients initially.

TABLE 1.—*Medical Specialties Involved in the Care of 16 Patients With Toxic Shock Syndrome at LDS Hospital, 1977 to 1983*

Specialty	*Number of Patients*
General practice	2
General internal medicine	7
Internal medicine subspecialties	8
Endocrinology, hematology, nephrology, pulmonary medicine, gastroenterology, rheumatology and neurology	
Infectious disease	13
General surgery	6
Surgical specialties	2
Orthopedics, vascular surgery and otorhinolaryngology	
Obstetrics/gynecology	6
Dermatology	2

TABLE 2.—*Proportion of Reported Toxic Shock Syndrome Cases of Patients Admitted to Hospital in Utah, 1976 to 1983*

	Year							
	1976	*1977*	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*
In-hospital cases	1	2	4	13	31	19	27	9
Total cases	1	2	5	14	50	21	33	9
(Percent)	(100)	(100)	(80)	(93)	(62)	(91)	(82)	(100)

Most reported TSS cases were admitted to hospital (Table 2). In an exceptional year, 1980, 38% were treated as outpatients or received no treatment at all. Most of these cases were self-reported.

As awareness of TSS has increased, it appears that fewer cases are referred to tertiary care hospitals for diagnosis and management. Before 1981, 6 of 52 (11.5%) of patients admitted to hospital statewide were transferred whereas since then only 1 patient of 55 (1.8%) has been.

The proportion of nontransferred cases receiving intensive care at the LDS Hospital has changed relatively little in seven years. Six of eleven patients began their hospital stay in special units. The length of stay in intensive care units has varied between one and five days. It has been declining since 1980. The duration of hospital stay has shown no consistent trend and has averaged 5.6 days.

The medical management of patients with TSS admitted to LDS Hospital has changed somewhat since the syndrome was publicized in 1980 (Table 3). The use of vasopressors, corticosteroids and blood or plasma (or both) has decreased significantly. Antibiotics were used for all cases before and after 1980, but the choice and number of drugs have apparently changed. Before 1980, all patients received antistaphylococcal antibiotics as part of empiric multidrug therapy. These included erythromycin (one), clindamycin (two), cephalosporins (two) and nafcillin sodium (one, in a patient who also received cefoxitin). Monotherapy with nafcillin was used only after 1980 and since then has been used in about half of the patients. However, 11 of 12 patients received nafcillin. The other patient was treated with a cephalosporin. Additional antibiotics were used in seven cases, but in two the sole additional agent was gentamicin sulfate, chosen because of possible synergistic antistaphylococcal activity.

Outcome

The overall case-fatality rate for TSS was 2 of 35 (5.7%) before April 1980 and 0 of 100 since. The case-fatality rate for patients admitted to hospital before April 1980 was 2 of 26 (7.7%) and 0 of 80 since ($P < .05$). Medical management of the early fatal cases included nafcillin, fluid replacement, vasopressors and removal of tampons that were used by these two menstruating women. One patient had an exploratory abdominal operation because of abdominal pains, but no abnormalities were discovered. Both patients were admitted to intensive care units and received the type of monitoring and supportive therapy used for subsequent cases admitted in these units.

Recurrence of TSS has also declined since 1980. Before then, 9 of 20 (45%) patients having menstrual TSS had a second episode within three months after the first, whereas since then only 8 of 100 (8%) patients with menstrual TSS have had a recurrence ($P < .05$). Experience at LDS Hospital suggests that this reduction in recurrence may be associated with the use of penicillinase-resistant β-lactam antibiotics. Two of seven (29%) patients with menstrual-associated TSS who received such therapy had TSS a second time compared with two of three patients who did not receive this class of drugs (P = no significance, Fisher's exact test). Antistaphylococcal β-lactam antibiotics were used for all of the nonmenstrual cases at the LDS Hospital. One of these, a woman with a staphylococcal pustule on her thigh evident during her first episode, was readmitted nine days after discharge with recurrent TSS and no apparent focus. She had received a two-day course of nafcillin, 12 grams per day, in the hospital, and then completed an eight-day course of dicloxacillin, 250 mg orally every six hours.

TABLE 3.—*Medical Therapy for Toxic Shock Syndrome at LDS Hospital, 1977 to 1983 (Patients Treated/Total Patients)*

Period	Type of Therapy				
	Vaso-pressors	Cortico-steroids	Blood and/or Plasma	Nafcillin Sodium Alone	Multiple Antibiotics
1977-1979 . . .	2/4	3/4	2/4	0/4	4/4
1980-1983 . . .	2/12	2/12	4/12	5/12	7/12

Discussion

Toxic shock syndrome was first recognized in Utah at about the same time as in other parts of the United States. The reported incidence in Utah, however, has been higher than in the nation as a whole both at the time the incidence was peaking nationally in 1980 and subsequently.[8] Better surveillance and reporting have been suggested as the reason for the higher sustained incidence in Utah. Our discovery of three unreported confirmed cases and four suspected cases at our own hospital suggests that reporting in the state is certainly not perfect, but similar case-finding efforts in other states can clarify whether our reporting is really superior. Active surveillance in Utah is most likely to identify in-hospital cases of TSS. Cases not identified as TSS and even TSS cases that do not come to the attention of infection control practitioners are less likely to be reported.

The sharp peak in the state's incidence in 1980 parallels that seen nationally. Certainly, some of the milder, outpatient, self-reported menstrual cases were recorded in that year in large part because of extensive publicity given then to TSS in the national and state media.[13] A less dramatic change in the incidence of cases admitted to hospital and a relatively constant rate of nonmenstrual cases also suggest this may be the case. On the other hand, changes in the use of tampons or the withdrawal of Rely brand tampons from the market (or both) may also have contributed to the decline in menstrual cases. The experience with menstrual TSS at LDS Hospital is interesting with respect to this possibility. The incidence of menstrual TSS actually varied relatively little between 1977 and 1983 except for 1980 when three nontransferred cases were diagnosed. Two of the patients were users of Rely tampons. Our retrospective search for TSS cases and our sustained interest in the syndrome since 1980 make it unlikely that the increase in cases detected at our hospital in 1980 was primarily due to publicity. Such a phenomenon could be due to an as-yet-unrecognized factor affecting incidence in 1980, coupled with the very frequent use of Rely tampons by menstruating women in Utah. Our previous controlled study,[14] however, while it did show frequent use of Rely tampons by control patients, showed significantly greater use in cases of TSS ($P < .005$; relative risk, 6.11). Regardless of the reason for the perturbation in the incidence of TSS in 1980, the Utah experience suggests that menstruation and probably tampon use remain important risk factors for this syndrome. Our data also suggest that the postpartum state and certain surgical procedures such as nasal procedures may be associated with

an incidence of TSS similar to that occurring in women of menstrual age.

The average age of menstrual, postpartum and postsurgical cases of TSS may simply be indicative of the average age of persons exposed, but the absence of a trend toward a higher age-specific attack rate in younger age groups is a bit surprising if antibody acquired in youth is presumed to be protective. Even more interesting is the paucity of spontaneous cases of TSS in children who often sustain skin lacerations and abrasions that are likely to be infected with *S aureus*.

The multisystem involvement characteristic of TSS was obvious in our cases but expected by virtue of a case definition that required involvement of at least three organ systems.[10] In addition to involvement of the systems specified in the definition, many of our patients with menstrual TSS complained of arthralgias, suggesting another direct or indirect target for the presumed toxin of TSS. None of these patients had arthritis, and staphylococcal joint infection was not suspected clinically. The involvement of mucous membranes in patients with TSS, particularly the genital mucosa, is emphasized by the observation that even patients without a vaginal focus of infection or menstruation did have some evidence of local reaction as manifested by an abnormal vaginal discharge.

The relatively steady incidence of nonmenstrual TSS cases at the LDS Hospital and their high proportion of total cases compared with the rest of the state suggest that a sustained high level of awareness of the various circumstances in which TSS occurs may lead to increased recognition of cases that are not "classic." If this is so, it also suggests that the actual incidence of nonmenstrual TSS is substantially higher than reported even in Utah and that these cases may be less often correctly diagnosed and reported than menstrual TSS. In a controlled study, physicians showed a bias toward diagnosing TSS in menstruating women.[15]

The high case-fatality ratio first associated with TSS undoubtedly resulted, in large part, from selective diagnosis and reporting of the most severe cases. Recognizing milder cases could be expected to reduce the ratio, as could understanding the cause of the syndrome and prescribing the proper treatment. It is interesting that the mortality for in-hospital cases in Utah is lower now than before April 1980. This may be due to earlier patient or physician recognition of the syndrome and timely admission to hospital. It seems less likely to be attributable to changes in patient management since this has changed very little over time. It does appear that recurrence of TSS has declined over time in Utah and quite possibly, as others have suggested, as the result of more rational selection of antibiotic therapy.[4] Recurrences of menstrual TSS have been explained on the basis of persistent vaginal carriage of staphylococci, cyclical bleeding and tampon use in women who are slow or unable to mount a protective immune response. Antibiotics might be expected to interrupt this pattern at least temporarily if they are successful in changing the vaginal carriage of staphylococci. Unfortunately, the effectiveness of parenteral drugs in accomplishing this has not been well documented.

While milder cases of TSS are now being recognized, this end of the spectrum is truncated because of the rigidity of the case definition. A sensitive and specific diagnostic test would clarify the range of clinical manifestations associated with infection by exotoxin-producing staphylococci. Although menstrual cases continue to predominate, the recent recognition of TSS following delivery, nasal and other operations poses a new and intriguing problem to those concerned with nosocomial infections.[9,16] The efficacy of parenteral antibiotic prophylaxis in preventing TSS has not been studied. Interestingly, it is not routinely used for most procedures after which TSS has occurred in Utah because of the low rate of bacterial infection associated with a clean surgical procedure and a normal delivery.

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Advances in the Treatment of Metastatic Prostatic Cancer

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Several exciting new forms of therapy for metastatic prostatic cancer have been introduced recently. Luteinizing hormone-releasing hormone (LH-RH) agonists paradoxically inhibit pituitary release of luteinizing hormone, resulting in a fall of serum testosterone to castrate levels within two to four weeks. These drugs have no cardiovascular side effects. A nonsteroidal antiandrogen, flutamide, may be as effective as orchiectomy in men with untreated metastatic disease and has the advantage of preserving potency in most men. In recent reports, combining the LH-RH agonist with an antiandrogen resulted in "total medical castration," which may substantially improve objective response rates and patient survival. Ketoconazole, an antifungal drug, also rapidly inhibits testicular and adrenal androgen synthesis and decreases plasma testosterone to castrate levels within 72 hours. In men with hormone-resistant disease, combination chemotherapy may produce an objective response rate of 50%. In men with severely painful bony metastasis, an inexpensive drug used in Paget's disease, etidronate disodium, may be palliative.

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Carcinoma of the prostate is the second most common form of cancer in the older male population; nearly 23,000 men die of the disease each year.[1] At present, most patients with newly diagnosed prostatic cancer have advanced disease, with about a third having distant metastases.[2]

Background

In the early 1940s the dependence of prostate function and prostatic cancer growth on the presence of sufficient levels of circulating androgens was recognized, and Huggins and coworkers reported dramatic subjective and objective improvement in several patients with terminal metastatic prostatic cancer by doing bilateral orchiectomies.[3] In addition, it was learned that endocrine therapy often provides relief of bone pain, anorexia and obstructive symptoms, regression of osteoblastic and pulmonary metastatic lesions and reduction in hydronephrosis caused by local extension of the tumor. Since then endocrine therapy has remained the cornerstone of first-line therapy in men with metastatic disease, and Huggins was awarded the Nobel prize in 1966 for his work.

Kinetic studies in experimental tumor models have shown that prostatic cancer is composed of a heterogeneous population of androgen-dependent and -independent cells.[4] Following androgen ablation (orchiectomy), androgen-sensitive cells regress. However, the residual androgen-insensitive cell population continues to proliferate slowly, often resulting in a patient's death. Following first-line endocrine therapy such as bilateral orchiectomies, there are residual circulating adrenal androgens. However, adrenal androgen levels are quite low, and adrenal ablation apparently does not result in further disease regression.

The various methods of hormonal manipulation used in prostate cancer therapy are shown in Table 1. These include ablating the source of androgen, inhibiting luteinizing hormone-releasing hormone (LH-RH) or pituitary luteinizing hormone (LH), administering antiandrogens—compounds that compete directly with endogenously produced androgens for receptor sites in the target tissue—and inhibiting androgen synthesis.[5] Some drugs have more than one site of action.

The most reliable form of hormonal treatment is bilateral orchiectomy, which represents the standard against which other forms of management are compared, in terms of both objective and subjective responses and of side effects. The advantages of bilateral orchiectomies include the following: the operation may be done on an outpatient basis under local anesthesia; serum testosterone levels are always reduced to

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ABBREVIATIONS USED IN TEXT

DES = diethylstilbestrol
LH = luteinizing hormone
LH-RH = luteinizing hormone-releasing hormone
NPCP = National Prostatic Cancer Project

castrate levels, usually within three or four days, and the side effects associated with estrogen therapy are obviated. However, some men have significant psychological trauma following castration. In such patients, leaving the epididymis, which has no hormonal function, may help alleviate patient reluctance to undergo gonadectomy; the epididymis is about the size of an atrophic testis.

Diethylstilbestrol (DES) is the least expensive (Table 2) and the most commonly used form of estrogen for managing prostatic cancer. Estrogens decrease androgen production by inhibiting LH release by the anterior pituitary (thus preventing testosterone production by the testis) and increase serum concentration of testosterone-estrogen-binding globulin, which decreases the circulating free testosterone. Side effects include gynecomastia (which may be reduced by administering low-dose radiation therapy to the nipples before initiating therapy), fluid retention, nausea and vomiting and an increased incidence of cardiovascular disease, particularly if 5 mg per day is taken. One disadvantage of DES therapy is that patients taking 1 mg a day do not always have sustained castrate testosterone levels throughout the day, although this may be alleviated by increasing the dosage to 2 to 3 mg a day in divided doses. In addition, testosterone levels do not drop as rapidly as they do following orchiectomy. Another disadvantage is that patients who experience relief of symptoms may not take the hormone on a regular basis as prescribed, simply because they feel better. Therefore, patient compliance is not as assured as it is with orchiectomy.

Following the initial evaluation of a case of metastatic prostatic cancer, indications for administering hormonal therapy are mostly subjective and include the bone pain, obstructive symptoms, anorexia, malaise or hematuria. The presence of significant anemia or hydronephrosis due to locally advanced disease also is an indication for promptly starting treatment. In asymptomatic patients, however, the decision whether to initiate hormonal therapy immediately or to wait until symptoms appear is left to the urologist. There is

TABLE 2.—*Cost of Hormonal Therapy for a Month*

Drug	*Dosage*	*Cost/Month*
DES	1 mg 3 times/d	$ 9.65
Estinyl*	0.05 mg twice/d	19.00
Premarin†	10 mg/d	36.45
Stilphostrol‡	50 mg 3 times/d	83.20
TACE§	12 mg twice/d	26.50
Emcyt‖	8 tabs/d	523.72
Ketoconazole	400 mg 3 times/d	227.70

DES = diethylstilbestrol

*Schering-Plough brand of ethinyl estradiol.
†Ayerst brand of conjugated estrogens.
‡Miles brand of diethylstilbestrol diphosphate.
§Merrell Dow brand of chlorotrianisene.
‖Hoffmann-La Roche brand of estramustine phosphate sodium.

no evidence that "early" hormonal therapy of asymptomatic patients results in better survival than "delayed" therapy.

Following either orchiectomy or DES therapy, 40% achieve complete or partial regression and 40% show disease stabilization.[6] The mean duration of response is about 90 weeks. Following further disease progession, as shown by worsening bone pain or new areas of metastatic disease, the mean survival is about six to ten months. Survival and objective response rates are not improved by combining orchiectomy and DES.

In the past decade, several new exciting agents have appeared that may have substantial impact on the future management of patients with metastatic disease.

LH-RH Agonists

In 1971 Schally and co-workers reported the isolation, description and synthesis of the molecular structure of the decapeptide luteinizing hormone-releasing hormone (LH-RH) (pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2).[7] Schally subsequently synthesized potent analogue agonists that possess 15 to 50 times more LH-releasing activity than the naturally occurring hormone.[8] The analogues were created by substituting a D-amino acid (alanine, *t*-butyl serine, tryptophan or leucine) for glycine in the sixth position of the decapeptide chain, removing the terminal amino acid and adding an ethylamide moiety to the proline at position 9. This results in increased affinity by the synthesized molecule

TABLE 1.—*Forms of Endocrine Therapy in Metastatic Prostatic Cancer**

Ablates Androgen Sources	*Inhibits Luteinizing Hormone-Releasing Hormone (LH-RH) or Pituitary Luteinizing Hormone*	*Antiandrogens*	*Inhibits Androgen Synthesis*
Orchiectomy†	DES†	Cyproterone acetate	Aminoglutethimide†
Adrenalectomy	Cyproterone acetate	Flutamide†	Cyproterone acetate
Hypophysectomy	Polyestradiol phosphate (Estradurin)	Medrogestone	Ketoconazole†
	Conjugated estrogen (Premarin)	Medroxyprogesterone	Medrogestone
	Medroxyprogesterone acetate (Provera)		Medroxyprogesterone
	DES phosphate (Stilphostrol)		Spironolactone
	Chlorotrianisene (TACE)		
	Buserelin acetate (LH-RH agonist)†		
	Leuprolide acetate (LH-RH agonist)†		

DES = diethylstilbestrol

*Some drugs have multiple sites of action.
†Treatments discussed in text.

to the pituitary receptor site. Schally received the Nobel prize in 1977 for his work.

The result of administering these analogues is that there is an abrupt increase in LH release and testosterone production. However, prolonged administration has the paradoxic effect of inhibiting pituitary release of LH (and follicle-stimulating hormone), resulting in a dramatic fall in serum testosterone levels. This probably results from pituitary depletion of LH with down-regulation of the hypothalamic-pituitary axis, desensitization of the testis to LH because of reduced gonadal LH receptor sites and possibly direct gonadal steroid enzyme inhibition. Serum testosterone is reduced to castrate level (60 ng per dl) within two to four weeks. All patients have a transient rise in plasma testosterone because of the initial pituitary stimulation.

We participated in a collaborative phase I study of one analogue, leuprolide acetate, to evaluate the side effects and efficacy of this type of drug. We found that 10% to 20% of men have a "disease flare" characterized by worsening bone pain and occasionally worsening hydronephrosis, probably due to the rise in serum testosterone levels. However, drug-related cardiovascular or thromboembolic problems and gynecomastia have been rare. About 50% to 75% have vasomotor hot flashes, and most have significantly diminished libido and erectile impotence.

As previously noted, the current standard of therapy is orchiectomy or DES and, as part of the National Prostatic Cancer Project (NPCP), we are participating in a prospective randomized trial, protocol 1700, comparing standard therapy with that using another LH-RH agonist, buserelin acetate, to determine whether objective response rates and survival are better with the experimental drug (Table 3). Although LH-RH analogues are administered subcutaneously, there has been excellent patient compliance. There is no known difference in hormonal response among various LH-RH agonists. Although the drugs are still investigational, the absence of significant side effects often associated with oral estrogen therapy makes them attractive possible substitutes.

Antiandrogens

A potent antiandrogen useful in metastatic prostatic cancer therapy is flutamide, which is a nonsteroidal drug. It neither inhibits gonadotropin secretion nor suppresses plasma testosterone, but appears to prevent binding of dihydrotestosterone to the nuclear androgen receptor. It may offer an additional advantage over conventional hormonal therapy in that potency appears to be preserved in most patients and there is no known cardiovascular morbidity.[9] Mild gynecomastia develops in most patients within two to eight months. Flutamide is still investigational and is being tested at several medical centers to determine its efficacy in men with untreated prostatic cancer. At present, it is unknown whether flutamide is as effective as orchiectomy or DES.

In an effort to prevent disease flare associated with the initial use of LH-RH agonists and to eliminate the effect of circulating adrenal androgens, Labrie and associates have reported adding an antiandrogen to the regimen when starting therapy.[10] They reported that not only do patients not have disease flare, but also there is a significantly higher objective response rate—nearly 100%—compared with 60% to 85% with conventional hormonal therapy. Although this is an exciting observation, it has not been substantiated by any other investigator. Their findings are controversial because men with locally advanced disease without distant metastasis are included. However, the NPCP has recently begun a prospective double-blind randomized trial, protocol 2200, to determine whether the combined form of treatment offers any advantage over conventional therapy.

TABLE 3.—*Current Protocols of the National Prostatic Cancer Project for Patients With Prostatic Cancer With Distant Metastases (Stage D2)*

Protocol Number	*Type of Study Patient*	*Treatments*
1700	Newly diagnosed stage D2	DES/orchiectomy *v* buserelin acetate (LH-RH agonist) *v* DES/orchiectomy + methotrexate
2200	Newly diagnosed stage D2	Leuprolide acetate + flutamide *v* leuprolide + placebo (double-blind study)
1500	Stage D2, hormone failure, no pelvic irradiation	Methotrexate *v* doxorubicin + cyclophosphamide *v* cisplatin + 5-FU + cyclophosphamide
2400	Stage D2, hormone failure, failure, with or without pelvic irradiation	Estramustine phosphate sodium (Emcyt) *v* flutamide

DES = diethylstilbestrol, 5-FU = 5-fluorouracil, LH-RH = luteinizing hormone-releasing hormone

Inhibition of Androgen Synthesis

Another class of drugs that may be beneficial in the endocrine management of prostatic cancer is the imidazoles. Ketoconazole is an orally administered drug that is used in the treatment of fungal infections. At high dosages it rapidly inhibits the production of both testicular and adrenal androgens by inhibiting enzymes necessary in steroidogenesis.[11] Early experience has shown that it decreases plasma testosterone to castrate levels within 72 hours, and objective response appears similar but not superior to orchiectomy. Although there are no feminizing or cardiovascular side effects, as many as half of patients may have significant nausea, necessitating reducing the drug dosage. Other imidazoles may be developed that have fewer side effects.

Chemotherapy in Prostatic Cancer

Chemotherapy has been reserved primarily for men who are clinically progressing following hormonal therapy. Through the efforts of the NPCP and other groups, several cytotoxic agents have shown efficacy in treating prostatic cancer, including methotrexate, cisplatin, cyclophosphamide, 5-fluorouracil and doxorubicin (Adriamycin) hydrochloride. If such agents are effective in men with end-stage disease, then they might be even more effective in patients with less tumor bulk. This was supported recently by Servadio and colleagues who reported a series of 24 patients with untreated metastatic disease undergoing orchiectomy, followed by administration of DES (3 mg a day), intravenous administration of 5-fluorouracil (10 mg per kg weekly) and cyclophosphamide (10 mg per kg weekly).[12] After two years, the chemotherapy doses were reduced by half and given every three weeks. Servadio and co-workers reported 75% stabilization or regression of metastatic lesions, which is similar to

results of standard hormonal therapy. However, the duration of survival appears to be improved, with a cumulative survival of 51% at six years, compared with a mean reported survival of three years in men with newly diagnosed metastatic prostatic cancer.[6] The NPCP currently is testing methotrexate as an adjuvant to hormonal therapy in men with untreated metastatic prostatic cancer (protocol 1700).

The National Prostatic Cancer Project was organized in 1973 and its initial endeavors focused on men with metastatic disease who had relapsed following hormonal therapy. In 1982 a phase III trial testing intensive outpatient combination chemotherapy in such men was initiated (protocol 1500). The three protocol arms include methotrexate (40 to 60 mg per m^2 given intravenously every two weeks); doxorubicin (50 mg per m^2 given intravenously every three weeks) plus cyclophosphamide (500 mg per m^2 intravenously every three weeks) and cisplatin (50 mg per m^2 intravenously every three weeks) plus 5-fluorouracil (500 mg per m^2 intravenously every three weeks) plus cyclophosphamide (500 mg per m^2 intravenously every three weeks). Toxicity has been acceptable. Preliminary results suggest that all of the treatment arms represent effective chemotherapy in prostatic cancer, with each arm eliciting an objective response rate of at least 50%.[13] With the support of referring physicians throughout the Northwest, our center consistently has led the NPCP in patient accrual. A more intensive phase I study conducted at Pennsylvania State University Medical Center (Hershey, Pa) using aminoglutethimide, cyclophosphamide, doxorubicin and 5-fluorouracil has shown an 81% objective response rate.[14] All of these patients have required some inpatient treatment, and a few have experienced considerable toxic reaction.

Palliative Therapy

Finally, patients who have already received hormonal therapy and are relapsing often have severely painful body metastases. Traditional methods of palliation have included administering steroids, radiation therapy (either directly to the painful site or half- or total-body irradiation), bromocriptine, adrenalectomy and hypophysectomy. More recently an inexpensive method of treatment was presented that may be effective.[15] Etidronate disodium (Didronel) is a diphosphonate and is quite similar in composition to pyrophosphates, which inhibit the precipitation of calcium phosphate and retard the conversion of amorphous hydroxyapatite into crystalline hydroxyapatite. Although pyrophosphates are rapidly inactivated by pyrophosphatase, diphosphonates are highly resistant to enzymatic hydrolysis and are potentially useful in the treatment of metabolic bone disorders. Etidronate disodium is a medication given orally and intravenously that acts primarily on bone and inhibits either bone resorption or bone mineralization. It is an effective, well-tolerated drug for the treatment of Paget's disease of bone,[16] with relief of bone pain in most cases. More recently, it has been reported to be quite effective in nine patients with various malignant disorders, including prostatic cancer, who have painful, bony, metastatic lesions.[15] Although etidronate disodium is not intended to cause disease regression, substantial palliative improvement has been reported. The Section of Urology at our center is participating in a randomized double-blind outpatient trial to determine whether early claims of the effectiveness of etidronate disodium are justified (Table 4).

TABLE 4.—*Etidronate Disodium (Didronel) Double-Blind Study*

Inclusion Criteria
Prostatic cancer with painful bony metastasis resistant to hormonal therapy or manipulation
Bone pain must be severe enough to require 40 grains of aspirin daily or its equivalent for pain relief. Patient does not need to be actually taking the analgesics
Exclusion Criteria
Patient with Paget's disease, which could confuse evaluation of the drug's effect
Serum creatinine level ≥ 2.5 mg/dl
Patients who have undergone irradiation of painful lesions within 4 wk of anticipated initiation of drug
Patients with change in hormonal therapy or chemotherapy within 4 wk of anticipated initiation of drug

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Kikuchi's Necrotizing Lymphadenitis

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Kikuchi's necrotizing lymphadenitis has recently been reported in the United States where it has not previously been recognized. In the past year three cases were seen in a community hospital in San Francisco. The histologic appearance and clinical features were felt to be sufficiently characteristic to be diagnostic.

(Evans CS, Goldman RL, Klein HZ, et al: Kikuchi's necrotizing lymphadenitis. West J Med 1985 Sep; 143:346-348)

Cases of Kikuchi's necrotizing lymphadenitis have been primarily reported in the Japanese literature.[1-3] The few descriptions in the English language literature have also originated outside the United States.[4,5] Recently, Turner and coworkers from Stanford University studied 30 cases of this disorder, 21 of which occurred in US residents.[6] The importance of recognizing the characteristic histologic appearance of this benign lesion is emphasized by the finding that 40% of their cases were originally diagnosed as malignant lesions, and 30% were subjected to further invasive procedures. In the past year we have diagnosed three cases of Kikuchi's necrotizing lymphadenitis in a community hospital. We report them to further document the occurrence of this disorder in the United States.

Reports of Cases

Case 1

A 34-year-old woman presented with a history of several months of painless enlargement of her right cervical lymph nodes. No clues were elicited by her medical history, routine laboratory studies gave normal values and on physical examination there were no other abnormalities found. A cervical node biopsy was done to rule out lymphoma.

Case 2

The patient, a 20-year-old woman, for 1½ months had slightly tender, right posterior cervical lymph nodes and transient low-grade fever. Treatment that consisted of administering cephalexin (Keflex) was unsuccessful. A medical history, routine laboratory studies and remaining physical examination elicited no abnormalities. A cervical node biopsy was done to determine the cause of her adenopathy.

Case 3

A 19-year-old woman for two to three weeks had enlarged right cervical and supraclavicular lymph nodes that did not recede with a trial of antibiotics. She also had a negative medical history, no constitutional symptoms, laboratory studies that gave normal values and results of a physical examination that were normal. A supraclavicular node biopsy was done to rule out lymphoma.

Pathologic Findings

All three nodes measured 1.5 to 2 cm in maximal dimension. The pink-tan cut surfaces showed no appreciable focal lesions. On microscopic examination there was a characteristic pattern of necrosis in each specimen (Figure 1). The capsules were intact and the architecture was variably altered by punctate cortical foci of necrosis. Within these foci, and representing a striking feature, was a conspicuous number of karyorrhectic nuclei, unassociated with a neutrophilic infiltrate (Figure 2). A polymorphous cellular population comprising histiocytes, foamy macrophages and small and large lymphocytes was present in and around the necrotic foci. This infiltrate was, however, notable for its paucity of plasma cells. Granulomatous inflammation and vasculitis were conspicuous by their absence. Stains for acid-fast bacilli and fungi were negative, and no viral inclusions were seen. The remaining nodal tissue contained residual lymphoid follicles with variable follicular hyperplasia.

Discussion

The histologic appearance of the specimens in our cases is identical to that described by Turner and associates and by numerous other authors, primarily in Japan.[1,2,5,6] The lesion

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consists of sharply demarcated paracortical foci of necrosis with karyorrhectic debris surrounded by a polymorphous mononuclear cell infiltrate. Plasma cells and neutrophils are scarce and there is no discernible granulomatous inflammation or vasculitis (Figure 3). The clinical features are also quite characteristic. Patients were almost invariably young women with cervical lymphadenopathy. None had a significant medical history and there were no systemic signs or symptoms except a transient low-grade fever in one patient. All of our patients remain well, although the follow-up interval ranges from 3 to 12 months, which is probably too short to be meaningful.

Figure 1.—Paracortical punctate necrosis surrounded by polymorphous infiltrate (hematoxylin and eosin stain × 40).

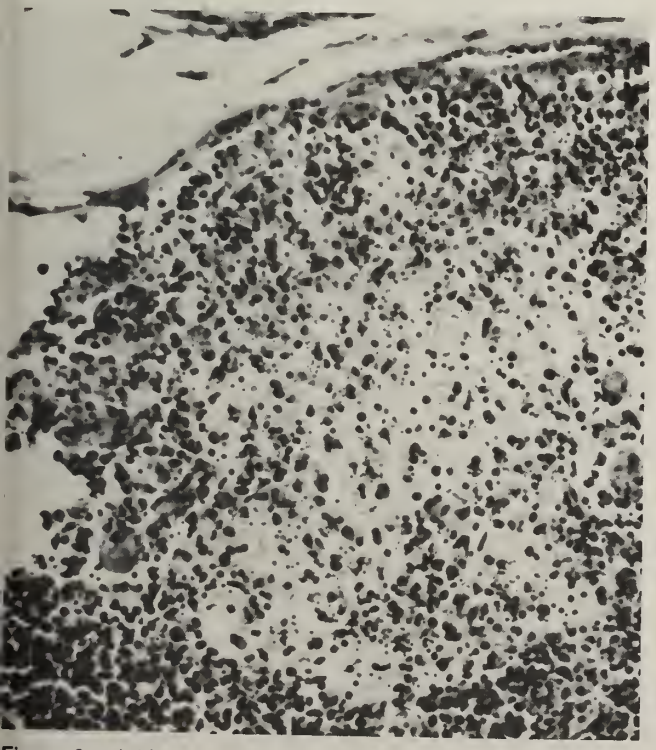

Figure 2.—A higher magnification (× 100) shows paracortical necrosis. Note superficial resemblance to germinal center with necrosis (hematoxylin and eosin stain).

Kikuchi's necrotizing lymphadenitis requires differentiating from malignant lymphoma with areas of necrosis and from other forms of lymphadenitis with necrotic features. In two of our cases the nodal architecture was preserved and was essentially normal. The remaining specimen was more extensively involved by necrotic foci, but residual lymphoid architecture remained intact. The associated cellular reaction around necrotic foci is characteristically polymorphous and lacks obvious nuclear atypia.

Other forms of lymphadenitis with foci of necrosis were considered. However, the histologic features were sufficiently characteristic to rule out animal scratch disease, lymphogranuloma venereum and caseous and gummatous types of necrosis. Systemic lupus erythematosus may present with cervical lymphadenopathy in a young woman. Histologically these nodes may show scattered focal necrosis and a variable percentage of cases will have tuboreticular structures on electron-microscopic examination.[7] The histologic features of the specimens in our cases were distinctly different, however, in that the nodal architecture was generally well preserved, there were no "hematoxylin bodies," the surrounding cellular infiltrate contained only rare plasma cells and there was no evidence of fibrinoid necrosis in the vessels.[7,8] Although none of the specimens was submitted for electron-microscopic examination, we emphasize that the histologic appearances alone, in conjunction with the clinical history—that is, in younger and essentially asymptomatic women—are distinct enough to allow diagnosis.

The cause of this particular form of lymphadenitis remains uncertain and may be multifactorial.[6] Ultrastructural studies have implicated a hyperimmune reaction that is, however, of a nonspecific nature.[7,9] Eimoto and colleagues found tubo-

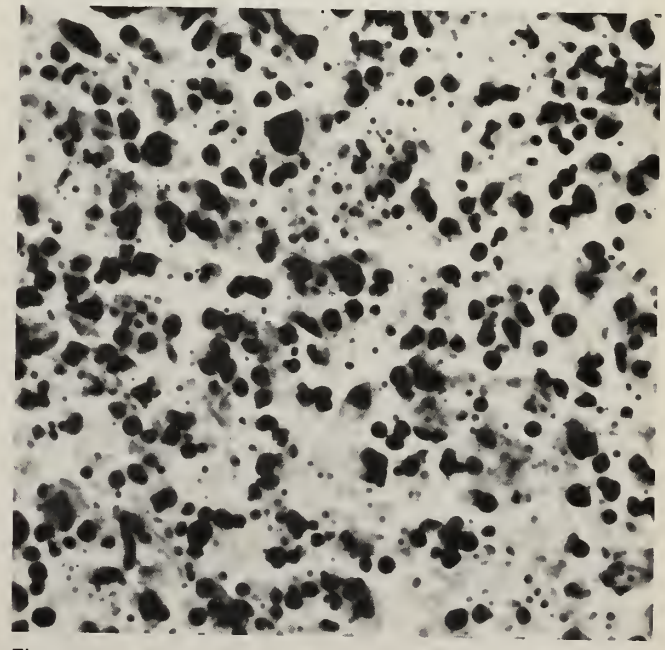

Figure 3.—Karyorrhectic nuclei and polymorphous infiltrate without neutrophils or plasma cells (hematoxylin and eosin stain × 400).

reticular structures and "intracytoplasmic rodlets" in a high proportion of cells in nodes showing Kikuchi's necrotizing lymphadenitis and in another form of necrotizing lymphadenitis with follicular hyperplasia that appears clinically to be a mild collagen disease, possibly related to systemic lupus erythematosus.[7] The recent provocative work of Feller and coworkers, who studied three patients with necrotizing lymphadenitis, should be noted.[4] All of their cases showed infection with *Yersinia enterocolitica*, type 3 or 9, and showed characteristic histologic changes affecting the paracortical T zones, and, more specifically, T-associated plasma cells immunologically characteristic of helper/inducer T cells. However, Kikuchi's necrotizing lymphadenitis does not resemble known cases of *Yersinia*-associated lymphadenitis.[4,6] The work of Feller and associates requires corroboration in future studies, and, as these authors state, not all cases of Kikuchi's necrotizing lymphadenitis seem to be due to *Yersinia*. To date, all reported cases have had a benign course, usually resolving within a few months. Until there is more experience with this disorder in the United States, however, these patients require long-term follow-up.

Finally, as there are other distinct necrotizing processes in lymph nodes, we, along with others, feel that the term "necrotizing lymphadenitis," used by Kikuchi in the Japanese literature, could be confusing and other suggested names have been cumbersome. Therefore, we refer to this lesion as Kikuchi's necrotizing lymphadenitis, as suggested recently by Dorfman and Turner.[10]

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Medical Progress

Screening for Developmental Disabilities

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Developmental disabilities are responsible for a combination of severe physical, mental, psychological and social deficits. They develop before age 22 years and involve a little more than 1% of the population. Screening for developmental disabilities is the first step in their prevention. Various screening instruments are available for use throughout the developmental years that are designed to detect the wide variety of developmental problems that interfere with a developing person's optimal adaptation to his or her environment. The screening instruments must be inexpensive, reproducible, widely available and cost effective to the child, family and society.

(Foster C, Duran-Flores D, Dumars KW, et al: Screening for developmental disabilities [Medical Progress]. West J Med 1985 Sep; 143:349-356)

Developmental disabilities are estimated to produce severe impairments in a little more than 1% of the population.[1] Many studies have shown improved outcomes for children with or at risk for developmental disabilities who are provided treatment at very early stages.[2] Because pediatricians and family practitioners are among the few professionals who, as a group, see almost all infants and young children, they play a major role in the early diagnosis of developmental disabilities. Their role in screening for many childhood conditions (for example, the federally mandated Early and Periodic Screening, Diagnosis and Treatment [EPSDT] program on screening for health assessments) is well understood, but their role in screening a child at risk for developmental disabilities is not as well defined. For a program to be effective, the screening procedures should be available for everyone at risk in the population. Ideally, the screening should be accomplished at a single contact with a child or family and with a minimum of cost and time. Unfortunately, a one-time screening effort for developmental disabilities is ineffective because the disabilities may emerge at any time during the developmental period, including the adolescent years, and present with diverse symptoms. A brief overview of the definition of developmental disabilities indicates the complexities of comprehensive screening.

Defining Developmental Disabilities

The category of developmental disabilities was first established in 1970[3] to encompass a broad spectrum of disorders, all of which result in children developing more slowly than their peers, acquiring fewer skills than their peers and requiring extensive support systems throughout their lives. To be eligible for services under the Developmental Disabilities Act, a person must fit the definition of developmentally disabled:

> The term 'developmental disability' means a severe, chronic disability of a person which
> 1. Is attributable to a mental or physical impairment or combination of mental and physical impairments;
> 2. Is manifested before the person attains age 22;
> 3. Is likely to continue indefinitely;
> 4. Results in substantial functional limitations in three or more of the following areas of major life activity:
>   a. Self-care,
>   b. Receptive and expressive language,
>   c. Learning,
>   d. Mobility,
>   e. Self-direction,
>   f. Capacity for independent living,
>   g. Economic self-sufficiency, and
> 5. Reflects the person's need for a combination and sequence of special, interdisciplinary or generic care, treatment or other services that are of lifelong or extended duration and are individually planned and coordinated.[3]

The above definition is a functional one because it identifies how a person carries out daily activities. While each state must follow this definition to obtain the federal funds, some states use slightly different versions. For instance, California uses a combination of categorical (describing the type of disability) and functional approaches. That is, a person with a substantial functional limitation is eligible only if she or he has mental retardation, cerebral palsy, epilepsy, autism or a related neurologic disability.[4]

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ABBREVIATIONS USED IN TEXT

CHDP = Child Health and Disability Prevention
DDST = Denver Developmental Screening Test
EPSDT = Early and Periodic Screening, Diagnosis and Treatment
IEP = Individual Educational Plan
PKU = phenylketonuria

Purpose of Screening for Developmental Disabilities

In this article we provide an overview of a broad-based screening program and describe the importance of a physician's role in that program.

Screening is the application of a simple accurate method for determining which children in a population are likely to be in need of special services to develop optimally. After screening, one can determine which persons should receive more extensive, more intrusive or more costly diagnostic procedures. Screening procedures should not be viewed as diagnostic, they simply divide a population into those who need diagnostic work and those who are not at risk for a condition. Diagnosis determines the extent and, in some cases, the cause of a disorder and is useful for making placement decisions.[5]

A broad-based screening program must include the functional, categorical and etiologic approaches. If only one or two of these approaches are used, eligible children may not be identified until major delays have occurred. Table 1 provides examples of how children at risk for different conditions may or may not be identified if the screening program assumes only a single definition or orientation.

For example, if one screens only for significant limitations, then phenylketonuria (PKU) will not be discovered until irreparable brain damage has occurred. Also, if one screens only for specific etiologic conditions, then many children with mental retardation, language delay and other conditions of unknown cause would be missed.

Characteristics of Screening Programs

Standard screening procedures should share common characteristics whether they are to screen for tuberculosis or for developmental disabilities. First, the screening procedures should be less costly in time, materials and other resources than the diagnostic procedures. If the resource requirement is essentially equal, then a professional should simply use an accurate diagnostic procedure.

Screening procedures should also be simple. An extremely difficult or painful procedure cannot be justified for every child when only 1 out of 10,000 may have the condition. Conversely, asking a 5-year-old child to respond to the Snellen E chart is simple for both the child and the professional.

A comprehensive program should also incorporate screening for conditions other than developmental disabilities. Including biomedical conditions such as sickle cell disease, psychological problems such as attention-deficit disorder and sociocultural problems such as child abuse greatly enhances the screening program.

Screening is appropriate whenever age of onset and duration of process aggravate or worsen the outcome. As with any behavioral trait, early identification or preventing its occurrence lessens the sequelae of complications. Just as proper eating habits ameliorate the occurrence of obesity and not starting to smoke is easier than stopping, early identification of those mechanisms responsible for failure of attentiveness or learning improves outcome. Medicine has learned that treating a case of tuberculin conversion is easier than waiting for the development of disseminated disease. Placing a newborn on a low phenylalanine diet prevents the occurrence of the devastating consequences of uncontrolled phenylalanine levels.

Related to intervention is the cost effectiveness of the screening procedures. Relatively costly procedures for extremely rare disorders need to be considered carefully. The cost of lead screening on the East Coast has been considered a worthwhile investment because of the incidence of lead poisoning there (Table 2). It is unclear whether or not this is an appropriate activity in many western states where young children's access to lead is limited. However, screening tests adequate for detection should be inexpensive, easily repli-

TABLE 1.—*How a Screening Program Can Be Affected By the Definitional Approach Taken*

Condition Identified	*Type of Definition*		
	*Functional**	*Categorical*	*Etiologic*
PKU	Discovered only after irreparable brain damage has occurred. A child with PKU is identified only when functional limitations are apparent.	Discovered only after irreparable brain damage has occurred. A child with PKU is identified only when mental retardation is apparent.	Discovered through a newborn screening program; damage can be prevented.
Mental retardation	Discovered through screening for functional limitations.	Discovered through screening for functional limitations.	Many etiologic conditions result in mental retardation, but if screening is done only on an etiologic basis, many are missed.
Substantial limitation in language and self-care associated with neglect and not associated with mental retardation, cerebral palsy, epilepsy or autism	Discovered through screening for functional limitations.	Discovered through screening but may not be eligible.	Probably not discovered by screening according to cause.
Lead poisioning	Discovered only after irreparable brain damage has occurred; a person with lead poisoning is identified only when functional limitations are apparent.	Discovered only after irreparable damage has occurred. A person is identified only when mental retardation is apparent.	Discovered through lead screening; further damage can be prevented.

PKU = phenylketonuria

*The functional approach is as laid out in the Developmental Disabilities Act of 1970.[3] In the State of California, functional limitations must be associated with mental retardation, cerebral palsy, epilepsy and autism.

cated and capable of being conducted by a health, educational or psychological assistant. The screening test should be accompanied by a minimum of false-positive and false-negative results. False-negative results (failing to refer persons who have the condition) should be avoided for conditions that are potentially devastating, such as those identified in biochemical newborn screening. Conditions that may result in negative labeling (poor environment) may require a more conservative approach to referral and have more false-negatives. In the latter instance, continued surveillance by a physician is important.

Screening tests imply surveillance of a large at-risk population, together with accurate diagnostic capabilities and effective intervention modalities or strategies. There are situations wherein screening is most successful within a limited population. For example, Tay-Sachs and sickle cell diseases occur in fairly circumscribed groups. A crucial decision is when the screening program should be applied. For example, screening for PKU, galactosemia and hypothyroidism during the newborn period identifies those at risk during the early period when treatment is most effective rather than, for example, screening at the preschool ages. Unless there are earlier clinical symptoms, screening for vision and hearing deficits coincides nicely with children's visits to physicians just before entering school. Referrals for further testing and intervention can follow. Using the latest technology, which will soon be available, screening for Huntington's disease during the newborn or early years is inappropriate for we have nothing to offer those who may be carriers and thus will ultimately be affected.

Screening for behavioral and cognitive end points must be interpreted very cautiously. Screening for development must be a collaborative venture between those testing a child and the child's guardian, usually the parents. A child who generally functions within normal limits may score in the questionable range for reasons of ill health, emotional stress, culture or language barriers. Intervention in the event that a child does not test within the normal range is carried out only after due collaboration with parents, health care providers or educators. This again emphasizes the fact that screening in no way implies a diagnosis, or that it should immediately be followed by an intervention or a prognostication. It should only trigger a mechanism in which a full evaluation of that child is done, including input from parents, guardian caretakers, educators or day-school personnel.

Screening for PKU in California provides an example of procedures that meet these considerations. By screening at birth in the hospital, the program reaches essentially all newborns. In California from October 3, 1980, to August 1, 1985, which includes 1,585,143 tests, there were no missed cases.[7] It requires little effort on the part of hospital staff. All infants with elevated phenylalanine levels are identified by the screening test; 1 out of 34 with an initial positive screen has classical PKU. The cost is $24 per infant tested, which is low when compared with the cost of at least $40,000 per year for adults with untreated PKU.[1] Finally, early diagnosis is extremely important. An effective dietary treatment can be instituted immediately, resulting in the child's maintaining normal intellectual functioning. This is in contrast to children untreated for even the first year of their lives, whose mental development will be retarded. There is a direct relationship between the length of time a child is untreated and the decrease in intellectual functioning.[8,9] Thus, PKU screening is available to all newborns and is accurate, simple, inexpensive and results in early effective treatment.

Recommendations for a Physician's Role in Screening

The physician's role in screening is especially important. As a provider who has regular contact with the family, the physician can monitor a child's development through routine screening. The role of physicians in preventing the occurrence of a developmentally disabling condition will be described at three developmental stages: preconceptual, prenatal and postnatal.

Preconceptual

The health of a newborn is to some extent related to the state of the mother's health. Certain safeguards for a newborn infant can be undertaken by the mother. It is hoped that the mother is in optimal health before and during her pregnancy. Table 3 lists those situations that increase a mother's risk for complications including the birth of a handicapped infant. A physician may wish to screen women for these factors and counsel them accordingly.

Though a mother affected with one of many chronic diseases can deliver a normal infant, there are disorders such as hypertension, diabetes, heart or renal disease and the like that increase her risks for complications. Optimally, before pregnancy all mothers should receive the rubella vaccine or have serologic evidence of rubella immunity (or both). The pres-

TABLE 2.—*Regional Screening for Lead Poisoning of Children Who Required Pediatric Management, October 1,1980, Through September 30, 1981**

Region†	Total Screening	Total Requiring Pediatric Care	Percentage (%)
I Conn, Mass, RI—6 programs	51,282	1,622	3.16
II NJ, NY—14 programs	171,728	8,786	5.12
III Del, Md, Pa, Va, Washington, DC—12 programs	84,195	3,722	4.42
IV Ga, Ky, SC, Tenn—4 programs	47,631	614	1.29
V Ill, Ind, Mich, Ohio, Wis—15 programs	108,430	5,087	4.69
VI Ark, La, Tex—4 programs	48,944	571	1.17
VII Iowa, Mo, Neb—5 programs	19,487	1,481	7.60
IX Calif—2 programs	4,033	9	0.22

*From the Centers for Disease Control, 1982.[6]
†No data are available for Region VIII.

ence of genetic disorders and maternal age influence the risks of being delivered of a handicapped infant. It is useful to know the blood and Rh type of the mother and, if the mother is blood type O, Rh negative or both, the father should be tested. In selected populations it is advisable for couples to have reproductive testing for sickle cell disease (in blacks), thalassemia (in Asians and Mediterranean population groups) and Tay-Sachs disease (in Jews).

Prenatal

Wilson[10] has listed genetic and environmental causes of developmental defects, as shown in Table 4.

A note of caution is necessary in interpreting this table. A developmental defect differs from a developmental disability. For example, cleft lip-cleft palate is a developmental defect, but in isolation rarely produces a developmental disability.

Earlier we mentioned the desirability of screening for the hemoglobinopathies and Tay-Sachs disease in appropriate population groups. As part of preconceptual or prenatal care, one should obtain a brief pedigree, inquiring specifically about fetal loss, malformations, mental retardation, short stature, myopathies and neuropathies and common disorders such as cystic fibrosis, Huntington's disease and other late-onset disorders. Based on this information and parental age, the following families must be notified about the availability of prenatal diagnosis for genetic disorders:

- The mother will be 35 years or older or the father will be 55 years or older at the time of the child's birth.
- Either parent has had a previous child with Down's syndrome or another chromosomal abnormality.
- There is a history of a relative with a proved possibly heritable chromosomal anomaly or mental retardation.
- The couple has a history of two or more miscarriages or infertility.
- Either parent carries a balanced chromosome rearrangement (inversion or translocation).
- There is a history of a congenital malformation in either parent or in a previous child.
- There is a family history of a neural tube defect such as spina bifida or anencephaly.
- Both members of the couple are carriers of an autosomal recessive disorder, such as Tay-Sachs or sickle cell disease, thalassemia or PKU.
- The mother is a known or possible carrier of an X-linked condition, such as Duchenne's muscular dystrophy, hemophilia A and X-linked mental retardation.
- Either parent is affected with or has been shown to carry the gene for an autosomal dominant condition, such as achondroplasia, Marfan's syndrome, tuberous sclerosis or neurofibromatosis.
- The mother has insulin-dependent diabetes mellitus, requires medication for epilepsy or has a history of other possible teratogenic exposure, such as rubella, x-ray or certain drug use during pregnancy.
- The parents are consanguineous (blood-related).
- There is reason to suspect fetal abnormality on the basis

TABLE 3.—*High-Risk Obstetric Patients*

- Socioeconomic
  - Age, younger than 18 years or older than 34 years
  - Parity, 0 or more than 4
  - Marital status, unwed
  - Below 125% of poverty level
  - Educational status, less than 12 years
  - Poor conditions for home delivery
- Nutritional
  - Weight falling outside of standard weight range
  - Hemoglobin, less than 10 grams per dl
- Past pregnancy performance
  - Difficult labor, prolonged (longer than 24 hours)
  - Previous cesarean section
  - History of postpartum hemorrhage
- Past pregnancy outcome
  - Fetal death (infant larger than 500 grams [1 lb 2 oz])
  - Neonatal death (infant larger than 500 grams [1 lb 2 oz])
  - Major congenital anomaly (incompatible with extrauterine life)
  - Low birth weight (less than 2,500 grams [5½ lb])
  - Three consecutive abortions (less than 500 grams)
  - Damaged infant (especially neurologic defects)
- Medical or obstetric complication, present pregnancy, including but not limited to
  - Preeclampsia, eclampsia
  - Genital herpes
  - Diabetes mellitus
  - Heart disease
  - Rh sensitization
  - Sickle cell anemia
  - Hemoglobinopathies
  - Renal disease
  - Mental retardation as evidenced by one of the following
    - Previous enrollment in a special education class
    - Evaluation by a state or federal department of vocational rehabilitation
    - Evaluation by a state or federal department of mental disabilities
    - Evaluation by a licensed psychologist
    - Substantial evidence of inability to manage daily self-care
  - Mental illness as evidenced by one of the following
    - Diagnosis from a psychiatrist
    - Evaluation by a mental health center
    - Evaluation by a psychiatric hospital

TABLE 4.—*Causes of Developmental Defects in Humans**

Defects		*Percentage (%)*
Known genetic transmission		20
Chromosomal aberration		3-5
Environmental causes		
Ionizing radiation		<1
Therapeutic	Nuclear	
Infections		2-3
Rubella virus	Varicella virus	
Cytomegalovirus	*Toxoplasma*	
Herpesvirus hominis	Syphilis	
Maternal metabolic imbalance		1-2
Endemic cretinism	Phenylketonuria	
Diabetes mellitus	Virilizing tumors	
Drugs and environmental chemicals		4-5
Androgenic hormone	Anticonvulsants	
Folic antagonists	Oral hypoglycemics (?)	
Thalidomide	Few neurotropic-anorectics (?)	
Oral anticoagulants	Organic mercury	
Maternal alcoholism		
Combinations and interactions		?
Unknown		65-75

*Estimates are based on surveys and case reports in the medical literature.

of other studies (ultrasound, maternal serum α-fetoprotein level or Rh titer).

Within the next 6 months, California will institute a statewide screening program for neural tube defects using maternal serum α-fetoprotein. This will be voluntary and will be carried out at 15 to 16 weeks' gestation. A blood specimen will be drawn in private offices and clinics and then forwarded to central laboratories. This will identify, in the tested mothers, 80% of the conceptuses affected with neural tube defects. The other 20% will not be detected as the sac on the back is covered with normal skin and will not allow the escape of α-fetoprotein-containing cerebrospinal fluid from the fetus to the amniotic fluid and eventually the maternal serum.

The environmental risks listed in Table 4 are self-evident. We cannot emphasize enough the importance of maintaining adequate medical records, especially those related to environmental mechanisms. In light of our present knowledge, environmental agents are responsible for but a small segment of developmental defects and an even smaller segment of developmental disabilities. However, practitioners must be cautious in prescribing drugs during pregnancy because, for a litigious-minded American public, lack of absolute proof that an agent causes a defect is not an adequate safeguard when a physician is faced with a lawsuit in front of a lay jury. We need only cite the enormous settlements awarded to patients and families who have a history of Bendectin* usage during pregnancy or paternal exposure to Agent Orange. These pending settlements occurred despite the fact that neither of these two agents is clearly identified as being embryotoxic.

*A combination drug by Merrell Dow, each tablet of which contains 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride.

Nonetheless, clear record keeping is essential in documenting the need for any drug, along with adequate information given to patients.

Maternal substance abuse, particularly alcohol, is a significant contributing agent to the occurrence of developmental disabilities in offspring. Fetal alcohol syndrome is estimated to be the third most common cause of developmental disabilities, with a frequency of 1:1,000 to 1:2,000 of live-born infants,[11] just a bit less than the incidence of Down's syndrome.

Though recreational and street drugs are not embryotoxic, addicting drugs such as heroin, methadone and so forth certainly produce addiction in newborns and endanger an infant's survival. Cigarette smoking probably does not cause developmental disabilities; infants born to mothers who smoke, however, are often of low birth weight with its attendant risks.

Postnatal

Physicians are the professionals most likely to detect early developmental problems. Table 5 contains recommendations for specific screening tests and their timing from birth through adolescence.

Physicians, or their assistants, should be familiar with these procedures, schedule them on routine visits and monitor each child's development longitudinally. As can be seen from Table 5, there is a variety of screening procedures; they include determinations of cognitive and motor development, nutrition and parenting skills, in addition to a child's physical state (Tables 6 and 7).

If the results of any of these procedures are questionable, the physician should either apply the appropriate diagnostic

TABLE 5.—*Recommendations for Screening Tests From Birth Through Adolescence*

	Months								Years						
Age of Person Being Screened:	*Birth*	*1-2*	*3-4*	*5-6*	*7-9*	*10-12*	*13-17*	*18-23*	*2*	*3*	*4-5*	*6-8*	*9-12*	*13-16*	*17-20*
Interval Until Next Exam:	*1*	*1*	*2*	*2*	*3*	*3*	*5*	*6*	*1*	*1*	*2*	*3*	*4*	*4*	*None*
Screening Procedures															
History and Physical Examination															
Developmental history and assessment															
Infant/child indicators of high-risk status*	X	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Dubowitz or comparable newborn evaluation†	X	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Evaluation of motor development‡	X	X	X	X	X	..	..	..	..	..	..	..	..	..	..
PDQ§ and DDSTǁ		..	..	..	X	..	..	X	..	..	X	..	..	..	..
Dental assessment		..	..	..	..	..	..	..	..	..	..	..	..	..	..
Nutritional assessment		..	..	..	..	..	..	..	..	..	..	..	..	..	..
Health education	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vision Screening															
Snellen or equivalent visual acuity test		..	..	..	..	..	..	..	..	X	X	X	X	X	X
Clinical observation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hearing Screening															
Audiometric		..	..	..	..	..	..	..	..	X	X	X	X	X	X
Nonaudiometric*		X	X	X	X	X	X	X	X	X	..	..	..	..	..
Laboratory Tests															
Hematocrit or hemoglobin		..	..	..	X	..	X	..	X	X	X	..	X	X	X
Urine dipstick or urinalysis		..	..	..	..	..	..	..	..	..	X	X	X	X	X
Newborn screening	X	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Free erythrocyte protoporphyrin									May be done only if health history warrants						

DDST = Denver Developmental Screening Test, PDQ = prescreening developmental questionnaire

*See Table 6 for full description.
†From Oubowitz and Dubowitz.[12]
‡See Table 7.
§From Frankenberg et al.[13]
ǁFrom Frankenberg et al.[14]

procedures or refer to the appropriate agency. The decision for referral depends on the state and how services are provided. In California, referral to a regional center for diagnostic testing initiates the entry into the service system. Other states have other systems. In general, a physician should have colleagues in physical therapy, occupational therapy, social work, nutrition, dentistry, ophthalmology, audiology, speech and language, education and psychology who can cooperate in diagnosis and the development of intervention strategies.

Another important role a physican provides is communication with the family. By treating screening as part of routine pediatric care, the physician will be communicating with the family on the child's development and will be orienting them towards prevention efforts. As the child grows, parents and physician will discuss motor development, the child's response to parents and the use of language. Parents are excellent observers of their children,[17] and discussion with them can augment the physician's perception of a child. In addition, discussions on development will make the need for further testing more understandable in those infrequent instances when it is necessary. Incorporating the parents' observations into the physician's screening results will involve the parents in the decision. More familiarity with development also provides a better basis for encouraging questions and discussion.

A related responsibility of the physician is preparing parents for the diagnostic testing and possible intervention. Parents should be informed of what to expect, how long it will take, whether or not pain is involved, what information will be obtained and so forth. A few minutes of discussion on a procedure such as the auditory evoked potential can greatly reduce apprehension and promote the physician's rapport with the family. The preparation of parents promotes their ability to prepare their child. Better prepared and calmer parents result in calmer children, thus facilitating more accurate results on many diagnostic tests.

TABLE 6.—*Criteria for Eligibility of High-Risk Infants for Regional Center Intervention Services**

- Medical Factors
  - Prematurity (less than or equal to 32 wk)
  - Postmaturity (greater than or equal to 44 wk)
  - Low birth weight (less than or equal to 1,500 grams)
  - Small for gestational age (Lubchenco Scale)
  - Assisted ventilation with persistent respiratory instability, including recurrent apnea
  - Prolonged hypoxemia
  - Prolonged hypoglycemia, hypocalcemia
  - Hyperbilirubinemia (greater than or equal to 15 mg per dl)
  - Seizures or transient neurologic signs (positive or negative) in first 5 days of life
  - CNS hemorrhage, grades 2-4
  - Confirmed correlating infections of the CNS (meningitis, encephalitis)
  - Multiple congenital anomalies requiring special services
  - History of maternal chemical exposure (alcohol, hydantoin, warfarin)
  - Abnormal neurologic findings in premature infants
  - Not significant if
    - atypical tone
    - asymmetry
    - startles and/or tremors
  - Significant if combined with
    - lack of or inconsistent visual pursuit
    - decreased popliteal angle
    - decreased mobility
- Clinical/Behavioral Factors
  - Persistent feeding problems (mechanical)
  - Persistent inability to self-calm
  - Erratic sleep-wake patterns
  - Persistent tonal problems
  - Continued evidence of delay in one or more developmental areas
- Social/Environmental Factors
  - Poor maternal-infant attachment
  - Prior family history of abuse/neglect (parents, other siblings)
  - Neonatal addiction or maternal history of substance abuse
  - Mother's medical or mental condition of a nature to require professional supervision and support to assure necessary child care (severe cerebral palsy, mental retardation, depression, alcohol abuse)
  - Maternal age is 16 years or younger†
  - Lack of or inadequate use of support systems (church, parents)†

In the opinion of an interdisciplinary team—such as a hospital discharge planning team or a Regional Center Developmental Disabilities intake team—the infant is considered to be at high risk for becoming developmentally disabled.

CNS = central nervous system

*Report of the Association of Regional Center Agencies Prevention Task Force.[16]
†May not be used as a single criterion.

Schools

The physician's involvement with the educational system is important because of the federally mandated screening program. Nationally, the federally mandated EPSDT pediatric screening program is designed as an ongoing federally funded source of medical checkups and care for all persons, 0 to 21 years of age, enrolled in a state medicaid program, namely, that for low-income families.

California operates its version of this program, Child Health and Disability Prevention (CHDP), which, as of 1981, includes EPSDT services and state-supported screening only, not diagnosis and treatment, for "income-eligible, non-MediCal" children.

TABLE 7.—*Normal Ages of Appearance and Disappearance of Neurologic Signs Peculiar to Infancy**

Response	*Age at Which Normally Appears*	*Age at Which Normally No Longer Obtainable*
Spontaneous stepping	Birth	2-6 wk
Positive supporting (neonatal type)	Birth	3-6 wk
Crossed extension (allongement croisee)	Birth	1-2 mo
Trunk incurvation	Birth	1-2 mo
Moro reflex	Birth	1-3 mo
Redressement du tronc	Birth	Variable
Leg flexion in vertical suspension	Birth	4 mo
Rooting	Birth	3-4 mo awake, 7 mo asleep
Palmar grasp	Birth	6 mo
Adductor spread of knee jerk	Birth	7 mo
Plantar grasp	Birth	9-10 mo
Tonic neck patterns (imposable)	2 mo	5 mo
Landau reflex	3 mo	12-24 mo
Neck righting reflex (imposable)	4-6 mo	12-24 mo
Positive supporting (weight bearing)	6 mo	(persists)
Parachute reaction	8-9 mo	Variable

*From Paine.[15]

The national EPSDT screening model promotes an interest in identifying recognizable pediatric disorders that interfere with health and development. The screening periodicity chart (see Table 5) indicates that a developmental history and assessment is a part of health-assessment procedures required of an examiner at each of the age levels, from birth through 21 years. All practitioners can obtain developmental data from simple techniques and communication skills.

A Denver Developmental Screening Test (DDST)[14] is the standard tool used by pediatric nurse practitioners and physicians to assess development in children from birth through age 6 years. Beyond 6 years of age, medical tests, clinical observations, home-school psychosocial adaptation and knowledgeable judgment are the health professional's tools of developmental assessment. The newly revised DDST, the DDST-R, is less time-consuming than earlier versions. Specifically, 12 items or fewer are all that are necessary to obtain a result on children up to the age of 6 years. Even more simply, a prescreening developmental questionnaire[13] can be given to parents to complete in a few minutes. It is a "prescreening" tool designed to select those children who should have a complete DDST. This questionnaire is extremely short and simple and uses parental reports. It can discriminate developmental lags and suggest more detailed screening. In later ages, collaboration among health and education professionals and parents is essential for an effective and efficient use of a physician's time. While most abnormalities are minor, pediatric nurse practitioners, on screening students in schools, do regularly refer children with greater health and developmental manifestations for possible diagnosis and treatment.

For a child identified after age 6 years, referrals to a special education program originate primarily from teachers, parents, nurses and classroom aides, but at present relatively few from physicians. A typical "child-study team" might be the first level of response to a referral. Consisting of an administrator, a registered nurse, the child's classroom teacher and an appropriate professional evaluator, the team will review a child's level of performance and determine possible eligibility for special education services. If so determined, a second-level assessment strategy will be orchestrated to obtain various evaluations and pertinent information for use in deciding on the most appropriate special education services. Participants on this latter team may include school personnel, outside physicians and clinics, therapists and parents. Following attaining their findings, an Individual Education Plan (IEP) is written by school district personnel, the classroom teacher, parents and others who will delineate the following: the special services required, such as diet, transportation, nursing care; the classroom environment for placement (a special day class, a resource specialist), and teaching objectives and methods planned for an individual child—that is, academic, vocational, sign language or braille. An annual review and a three-year follow-up IEP meeting shall follow to evaluate case management.

The message to physicians from professionals in the fields of early childhood education and special education is to be aware of what a public school can and cannot do, along with what a medical practitioner can and cannot do. Basically, local school districts are able to take referrals on a child and determine a student's eligibility for certification as a "child with exceptional needs" for any child between the ages of birth and 21 years. They can also coordinate this process for the child and parents.

The physician can request an assessment of the child's performance and eligibility for "special services" by contacting a county Office of Education, local school district office or a school principal. A physician should look with sensitivity and scrutiny at a child's developmental history and current state and should engage the child *and* the parents in obtaining information to document physical and behavioral elements of each young patient. Physicians can cooperate by communicating via records and personal correspondence to schools, professionals and parents and can become providers of service in the state EPSDT program. Physicians cannot make promises to parents of educational services and special education placement and cannot be negligent by excusing parental concerns and clinically suggestive signs as "something the child will grow out of."

Concerned professionals should make a concerted effort toward an ongoing exchange of information about possible and known exceptional needs of children. The treatment and education of a child with special needs of a physical or a mental nature require the roles of various personnel. Unless all professionals share information and decisions for appropriate intervention, optimal comprehensive care will be unlikely.

Characteristic of uncoordinated client activities are fragmented interventions, gaps in service delivery, costly duplication and ill-advised services, poor child adaptation and parental and professional frustration. A team approach can guard against such problems and ensure that each child is given the opportunity to develop to his or her maximal potential.

Measures of Effectiveness

Evaluating any major social program such as screening for developmental disabilities has some major problems. We propose three general categories for evaluating the effectiveness of screening programs: quality of life, the incidence of developmental disabilities and the cost to society. These range from extremely subjective to quite objective. The most subjective, but perhaps the most important, is improved quality of life for a person and family. While having a developmental disability does not reduce the worth of a person, most people would agree that a developmental disability creates many personal, family and societal problems. Weikart[18] reported a reduction in several major social problems, including teenage pregnancy, unemployment, detention and arrest and welfare assistance for children who had been in a Head Start program 14 years earlier.

Another effectiveness measure that is more scientific but still difficult to obtain is the incidence of developmental disabilities. Determining the reduction in incidence of discrete conditions such as infants with rubella syndrome is complex but can be done with considerable accuracy.[19] The problems with ascertaining decreases in developmental disabilities are exacerbated by several issues. First, developmental disabilities represent a collection of conditions of both known and unknown causes. Due to the different definitions, this collection changes from state to state and even with the diagnostic instrument used. This changing definition creates difficulties in making comparisons across locations and time.

Another difficulty in evaluation is that the definition is relatively new. Since the category was created in 1970, there are no longitudinal data available. Related to this is the fact that because more money and more programs are available for persons with this diagnosis, more are identified.

Still another difficulty is presented by the fact that developmental disabilities can emerge any time during the developmental period. Thus, determining the counts at times when infants and children can be more easily evaluated, such as in screening for PKU at birth, may miss many children affected with other disabilities.

A more concrete measure of effectiveness can be found in ascertaining the cost of various conditions to the state or to the family. All states except two have mandatory screening for PKU, which affects about 1 in 17,000 births. In California, about 20 to 25 cases are detected each year.[7] Since 1966 when the program began, there has not been a single admission to the state hospital system. A conservative cost-benefit analysis shows that about $7 are saved for every dollar spent.[7] Estimates of how much the care of a child with developmental disabilities costs above that for a child without this condition are available. For example, according to the California State Council on Developmental Disabilities, it costs $360 per month to keep a child of 3 years at home (James Shorter, Executive Director, written communication, August 1984). The cost varies with size of family, age of child and gross income. If a child has a developmental disability and is placed out of the home, the cost can be as high at $6,000 per month (J. Shorter, written communication, August 1984).

The effects of screening and early intervention have also been documented through cost analyses. Children who received two years of preschool saved more than seven times the cost of the preschool for their public education compared with a matched control group.[18] Wood[20] analyzed costs and found that the cost of education for 940 multiply handicapped children depended on the age at which intervention was started. The cost was $37,273 for children who began programs at birth, compared with $45,816 for those who started at age 6 years.

The human impact is even more important than the financial aspects. The High/Scope Education Research Foundation found that children in the Head Start program experienced changes that were evident even after 12 years of public school. These children were more likely to finish high school, get a job, enroll in postsecondary education and score well on tests of functional competence than their matched peers who had not attended Head Start.[18] They were less likely to require special education, be arrested, be on welfare or become pregnant during the teen years. Other studies have shown changes in intelligence,[21] ability to adapt to regular education[22] and the ability to be self-supporting.[23,24]

Another area where early intervention has proved to be quite effective is in follow-up programs for high-risk infants from neonatal intensive care units. In California where these projects have been conducted on a pilot basis, there are significant reductions in child abuse, in the length of the original hospital stay and in the rate of readmission to hospital.[25]

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Specialty Conference

Lead Intoxication in Children

Moderator
WILLIAM L. NYHAN, MD, PhD

Discussants
MARK SAWYER, MD; THOMAS KEARNEY, PharmD; SAMUEL SPECTOR, MD, *and* SASKIA HILTON, MD

From the Departments of Pediatrics and Radiology, University of California, San Diego, Medical Center and School of Medicine, and Regional Poison Center Emergency Medicine Services, San Diego.

WILLIAM L. NYHAN, MD, PhD:* *Lead poisoning continues to be a significant source of morbidity in children. Promptly recognizing early symptoms and combining effective chelation with the removal of lead from a child's environment are associated with a good prognosis. Therefore, it is important for physicians to be alert to the possibility of this diagnosis. At the same time, although it is often thought that this is a problem found exclusively in the residents of very old buildings in the inner cities of the eastern part of the country, children in the West do get exposed to lead. There are even some unique or at least novel ways in which this takes place.*

Our experience with lead intoxication is increasing. In the period from July 1, 1983, through September 30, 1984, five patients with lead poisoning were admitted to the University of California, San Diego (UCSD), Medical Center. The reasons for this are probably complex and are not completely clear. In the cases to be presented at this conference, two of which are described in detail, the mechanisms of intoxication were well defined, but this is not always the case. Possibly more children are now living in old inner-city buildings in San Diego.

Reports of Cases

Case 1

MARK SAWYER, MD:† Two patients with lead intoxication were admitted to Childrens Hospital during the past year. The first, an 8-year-old Mexican girl, was well until a week before admission when abdominal pain developed. This was followed by fever, nausea and frequent emesis. She was treated with aspirin and ampicillin. On the day before admission she had a generalized seizure. She was initially admitted to hospital in Mexico. During the evening before admission her level of consciousness decreased and she became combative. She was given dexamethasone and transferred to Childrens Hospital in San Diego. It was learned that she lived next to a battery-processing plant in Mexico.

On physical examination she was lethargic but combative and appeared small and malnourished. Her respirations were 20 per minute; pulse 120 beats per minute and blood pressure 160/110 mm of mercury. Temperature was 37.9°C (100.2°F) rectally. She weighed 23 kg (51 lb). The pupils reacted sluggishly to light but the fundi were normal. The abdomen was soft. Her gaze was disconjugate. Results of a cranial nerve examination otherwise showed no abnormalities and sensorimotor findings were normal. Reflexes were normal. Laboratory evaluation showed a blood lead concentration of 62 μg per dl and a free erythrocyte protoporphyrin (FEP) value of 316 μg per dl of whole blood. Hemoglobin was 12.6 grams per dl, hematocrit 34% and mean corpuscular volume (MCV) 80 cu microns. Basophilic stippling was present in the erythrocytes. The leukocyte count was 18,300 per μl with 84% polymorphonuclear leukocytes, 7% bands, 8% lymphocytes and 1% monocytes. The specific gravity of the urine was 1.018 and there were 3 + ketones, 1 + blood, 2 to 5 leukocytes and 0 to 2 erythrocytes. The blood urea nitrogen (BUN) level was 20 and creatinine 1.1 mg per dl. The cerebrospinal fluid concentration of glucose was 92 mg per dl and protein 20 mg per dl; there was 1 lymphocyte.

An endotracheal tube was inserted, she was hyperventilated and an intracranial pressure monitor was placed. A computed tomographic scan of the head showed small ventricles suggesting diffuse edema. The initial intracranial pressure was 40 torr. It responded rapidly to treatment with barbiturate and mannitol and was easily maintained at less than 20 torr. Chelation therapy was begun using dimercaprol (BAL), 600 mg per day (720 mg per m^2), and edetic acid (ethylenediaminetetraacetic acid [EDTA]), 1,800 mg per day (2,170 mg per m^2), for five days. Her urinary excretion of lead was 3.7 mg per dl during the first 24 hours of therapy. The blood concentration of lead ten days after chelation therapy was 22 μg per dl. An electroencephalogram showed

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(Sawyer M, Kearney T, Spector S, et al: Lead intoxication in children—Interdepartmental Conference, University of California, San Diego [Specialty Conference]. West J Med 1985 Sep; 143:357-364)

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ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
EDTA = edetic acid (ethylenediaminetetraacetic acid)
FDA = Food and Drug Administration
FEP = free erythrocyte protoporphyrin
MCV = mean corpuscular volume
UCSD = University of California, San Diego

generalized slowing. Treatment was continued with phenobarbital.

She was seen three months after discharge and had a blood lead concentration of 42 μg per dl and an FEP value of 424 μg per dl. She had evidence of peripheral neuropathy with left foot drop. A sample of water from her home supply had an extremely high lead content.

Case 2

The patient, a 15-month-old Mexican female infant, was in excellent health until two months before admission when diarrhea developed. She was initially treated with ampicillin and after failing to respond was given azarcon for five days. Her 3-year-old sibling was given the same medication, progressive lethargy and vomiting developed and she died two weeks later. For this reason, this child presented for evaluation. Although she was asymptomatic, her blood lead concentration was 124.5 μg per dl and the FEP value was elevated.

On physical examination on admission she was well developed and well nourished, her height was 64.5 cm and weight 10.4 kg (23 lb). Blood pressure was 100/45 mm of mercury, respirations 32 per minute, pulse 116 beats per minute and rectal temperature 38°C (100°F). The fundi were normal. The abdomen was unremarkable. She was alert and cooperative, and the sensorimotor examination elicited no abnormalities. Deep tendon reflexes were 2+ and symmetric and the cranial nerves were intact.

Laboratory evaluation elicited the following values: a hematocrit of 31.3%, hemoglobin 9 grams per dl, MCV 63 cu microns, mean corpuscular hemoglobin 18.6 cu microns, mean corpuscular hemoglobin concentration 29.7% and platelets 461,000 per μl; leukocytes were 14,900 per μl, with 33% neutrophils (2 bands), 58% lymphocytes, 4% monocytes and 2% eosinophils. Basophilic stippling was present. The reticulocyte count was 0.8%. The urine specimen showed a specific gravity of 1.020 and tests for protein, glucose and blood were negative. BUN was 16 mg per dl and creatinine 0.5 mg per dl.

Treatment was started with dimercaprol, 240 mg per day (800 mg per m^2) for three days, and EDTA, 390 mg per day (1,300 mg per m^2) for five days. Her blood concentration of lead fell to 61 μg per dl after five days of therapy. After discharge she received penicillamine, 375 mg per day (36 mg per kg of body weight per day), for five months. Her blood lead concentration at the time of discharge was 41 μg per dl.

Sources of Lead Contamination

DR NYHAN: *Dr Kearney will now present some very interesting information he has uncovered on the sources of the intoxications in these two children.*

THOMAS KEARNEY, PharmD:* Of paramount importance in the management of lead poisoning is identifying the source of the lead. These cases show some unusual sources of lead contamination in patients coming from Mexico. Of course, these hazards may affect our own citizens visiting Mexico and those who live here but who share cultural backgrounds with those across the border.

The causative agent in one patient was azarcon, which can be purchased in Tijuana. Azarcon is a bright orange powder used by the local folk healers or *curanderos* to treat nonspecific gastrointestinal symptoms known collectively as *empacho*. Azarcon is essentially 100% lead tetroxide and has a 90% content of elemental lead. There have been numerous instances of lead poisoning attributed to the use of azarcon reported in California and in Colorado.[1,2]

We recently carried out a screening project for lead on 100 Hispanic children in a San Ysidro clinic. The parents of the children screened for lead were surveyed with respect to their knowledge and use of folk remedies. A significant percentage of the parents (more than 10%) knew of azarcon and most of them said that they would consider using this substance for the treatment of *empacho* in their children.

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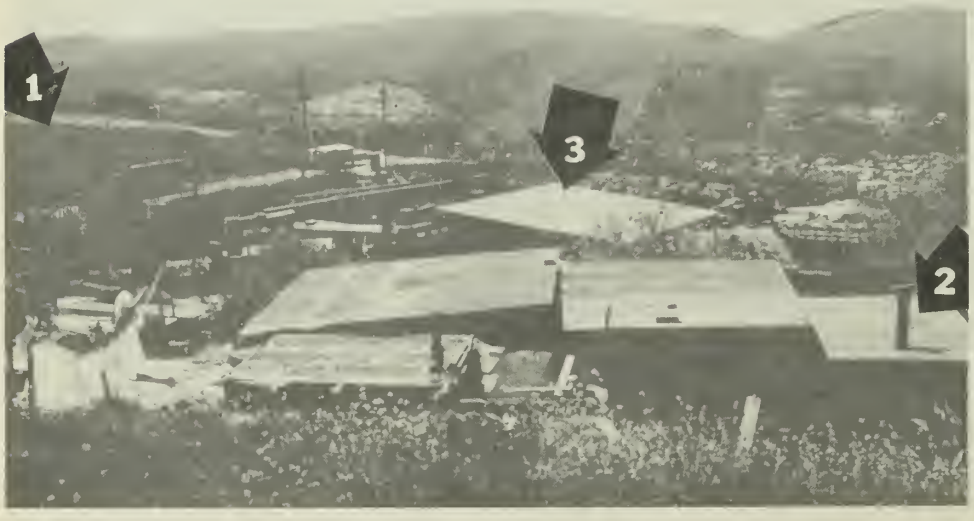

Figure 1.—La Gloria is a rural community located on a hillside. Adjacent to the community is the Rotary Club (arrow #1) where the horses died. This is a view looking down on the patient's residence (arrow #2). Arrow #3, battery recycling plant.

Apparently it is common practice among the Mexican-American community to seek medical attention from a folk healer or *curandero* in Mexico for the treatment of *empacho*. The folk healer usually resorts first to herbal teas in the treatment of diarrhea but administers azarcon in refractory cases. To increase the palatability of azarcon, it is usually mixed with an herbal tea or administered in dry powder form with sugar. The substance administered to our patient admitted to University Medical Center was a fine yellowish powder. This suggests that it may be lead oxide instead of lead tetroxide. Toxicologic analysis by atomic absorption spectrophotometry showed a 95% content of lead. This form of lead has been referred to as *greta*. The Food and Drug Administration (FDA) has reported that *greta* has been imported from Mexico and has been sold in Hispanic communities throughout southern Texas, Florida and California.[3] Other names such as *rueda, Maria Luisa* and *coral* have been given to these lead-containing folk remedies. The Centers for Disease Control have recommended that if patients of Mexican origin present with anemia, abdominal pain, peripheral neuropathy, encephalopathy or renal disease, lead poisoning from these home remedies should be considered in the differential diagnosis.[1]

Figure 2.—The residents just before our arrival had been warned about the potential for contamination of water and were drinking bottled water. The middle barrel in the figure held the drinking water primarily used by our patient.

In the first patient, the only relevant history at the time of admission was that the patient resided in close proximity to a battery recycling plant. Information was obtained that a Rotary Club that was also located nearby had reported that a couple of horses had died. This patient became our index case and it was imperative to identify the source of lead contamination, not only to prevent reexposure but to identify others at risk. A Mexican physician and I, with the assistance of a relative of the patient, did an on-site investigation of the patient's residence. The patient lived about ten miles south of Tijuana in a community known as La Gloria. As we drove in, we saw piles of batteries stacked 3 to 6 m (10 to 20 ft) in height all along the roadside leading up to the patient's residence (Figure 1).

Looking down on the patient's residence, we noted that there was a complete lack of electricity in the area and water was obtained primarily from collected rain water and stored in barrels and cisterns (Figure 2). Rain water was collected also on the roof, ran down a trough into barrels and was the primary source of water for drinking, bathing and other needs. The patient's house was located 46 m (50 yd) from the battery recycling plant. We interviewed the patient's grandmother and some neighbors. We looked for other possible sources of lead contamination in the home such as paint chipping from the wall or the use of earthenware pottery but found none.

In a survey of the neighborhood, we found that many children were experiencing nonspecific gastrointestinal symptoms and they had complained also of acid burns on their feet from open pools of discarded battery acid near the plant. The residents of the area had previously owned a variety of livestock, which had recently died. We also noticed a number of dead birds around the community.

The battery recycling plant used an open furnace to melt down the battery matrix. The impurities were separated from the molten matrix and the lead re-solidified and sold to a battery manufacturer. The exhaust pipe from the furnace was pointed directly at the patient's residence, fewer than 64 m (70 yd) away (Figure 3). The residents did complain about a

Figure 3.—The patient's house was located only 46 m (50 yd) from the battery recycling plant, Metales y Derivados de Tijuana. The plant used an open furnace to melt down the battery matrix. Note that the exhaust pipe from the furnace is pointed directly at the patient's residence less than 64 m (70 yd) away. Arrow #1, Rotary Club; arrow #2, cistern for water storage; arrow #3, furnace.

metallic taste, choking and coughing during the operation of the plant as well as discoloration of the soil.

Located in front of the house, near the plant, was a cistern that served as another storage area for drinking water for the family and its livestock. A specimen of this water was obtained from the cistern. A water sample was obtained as well from a neighbor's cistern because another child there had complained of gastrointestinal symptoms. The family before our arrival had been warned about the potential contamination of their water and were drinking bottled water. A specimen was obtained from the barrel containing rain water, and a final specimen was taken from the bottled water they were presently using.

Analysis of the lead content in the samples was done by atomic absorption spectrophotometry. For a frame of reference, San Diego water contains less than 1 μg per dl of lead. Analysis of the water samples from the patient's residence showed the following:

	Lead Content (μg per dl)
Front cistern	153
Barrel	1,080
Bottled water	4
Neighbor's water	69

It was reasoned that airborn lead effluent from the open furnace contaminated the water supply. We contacted public health officials and this resulted in closure of the plant.

Radiology

DR NYHAN: *Roentgenographic aspects will next be considered by Dr Hilton.*

SASKIA HILTON, MD:* Lead toxicity may cause a confusing array of gastrointestinal symptoms, including abdominal pain, anorexia, nausea and vomiting and constipation.[4] Unfortunately, unless symptoms of involvement of the central nervous system develop or a suggestive history is elicited, the nonspecific gastrointestinal complaints rarely point towards the diagnosis. Occasionally, plain films of the abdomen are taken for the evaluation of gastrointestinal symptoms and the films show paint chips or other evidence of pica such as ingested dirt or plaster. In our third patient, *greta,* the material administered, is readily visualized.[5] It is fortunate that most children with plumbism ingest the substance containing lead, as the lead is often radiographically visible. Identifying the site of the lead is often therapeutically helpful, especially if some or all of recently ingested lead remains in the gastric fundus and thus is available for removal by gastric lavage. In most cases, the offending agent is identified in the colon and can be removed by enema. Water enemas may be contraindicated in patients with increased intracranial pressure, but enemas can be undertaken using a hyperosmolar contrast agent. Fluids are drawn into the colon and mild stimulation of the colon results in evacuation. Patients with cystic fibrosis and

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Figure 4.—*Greta* is seen throughout the colon to the level of the splenic flexure. Numerous metallic densities of different sizes indicate that a large amount of lead is present in this patient.

Figure 5.—This supine x-ray film of the abdomen was taken of a 3-year-old boy who had ingested lead-based plaster. Densities are seen throughout most of the colon.

severe constipation or even intestinal obstruction are successfully treated with hyperosmolar enemas and so are neonates with meconium plug syndrome.

Plain films of the abdomen in the third patient (Figure 4) showed a large amount of mottled metallic density throughout most of the colon. The high lead content of *greta* is responsible for this appearance. The appearance differs from that in another patient we recently saw who had ingested plaster containing lead-based paint (Figure 5). Use of lead-based paint for commercial surfaces has greatly tapered off since about 1960. Interstate shipment was banned in 1977. However, fresh paint in older buildings does not protect children against ingesting plaster soaked with lead deposited from earlier coats of paint.

Discussion

SAMUEL SPECTOR, MD:* I thought when I left the Midwest that I would no longer encounter lead encephalopathy. Therefore it is surprising that we are discussing the cases of two patients seen at Childrens Hospital in San Diego and currently there is another patient at the UCSD Medical Center. Two of these three patients have shown clinical encephalopathy.

The patient recently admitted to the UCSD Medical Center is an 8-year-old Hispanic boy who had been receiving *greta* for one month before admission because of chronic abdominal discomfort. On admission, he was lethargic, hypertensive and constipated. He could not recall his home address or his telephone number, both of which he had known in the past. His blood lead concentration was 92 μg per dl.

The relationship of lead poisoning to environmental contamination has been well documented over the centuries. It is interesting to review the lead content in the sequential layers of ice in Greenland to obtain a profile of atmospheric contamination over time. At the beginning of the industrial revolution in about 1780, a gram of ice contained about 10 pg of lead. In 1980, levels reached 200 pg per gram, with the greatest increase occurring after 1940. In addition, the lead:calcium ratio of human bones from premetallurgic Peru, when compared with those of contemporary American adults, showed a 200-fold to 600-fold increase.[6] In this country, 1½ million tons of lead are processed each year, primarily in the manufacture of batteries and, secondly, in the petroleum industry in producing leaded gasoline. Lead poisoning as a major problem in children became evident initially in our inner cities. The reason was poor housing in which old, peeling internal paint contained high concentrations of lead. One flake could contain as much as 100 mg of lead. Between 1960 and 1966 in New York and Chicago, 3,339 patients were found to have lead poisoning, chiefly preschool children who had pica. The mortality rate was 8%. It is most upsetting that some 20 years later, screening of 500,000 urban children in 1981 still disclosed 23,000 children with lead poisoning. Although the lead content of paint is currently limited legally to less than 0.06%, old buildings with old, peeling paint remain. Dust has become an added factor, from destruction of buildings and exhaust emissions generated by heavy traffic. Dust contaminates the soil and vegetation and in small children it is placed in the mouth and also inhaled. In the most recent National Health and Nutrition Examination survey between 1976 and 1980, it was found that 4% of all children aged 6 months to 5 years in the United States had a toxic lead concentration in the blood of more than 30 μg per dl. The figures were 2% in rural areas and 11.6% in the inner cities.[7] An unexpected finding was that black people of all ages had significantly higher lead concentrations in their blood. Mean lead concentration in the total population was 14 μg per dl. Black preschool children in an urban setting had an average level of 22.9 μg per dl, compared with white children in whom the value was 18.1 μg per dl.

In reviewing sources of lead in the environment, the data of Chisolm and Barltrop are very useful (Table 1).[8]

In adults, 5% to 10% of ingested lead is absorbed from the gastrointestinal tract. In small children, absorption approaches 40%. In both children and adults, 40% of inhaled lead is absorbed from the respiratory tract. Furthermore, adults can excrete maximally as much as 500 μg of lead daily, while toddlers can excrete only 30 μg a day. Thus, it is clear that children have a special vulnerability. The nature of the sources and the behavior of young children who put virtually anything in the mouth explain why lead poisoning is predominantly a problem of the young. The first patient presented at great risk because she lived in close proximity to a battery factory. There was documented contamination of the water

TABLE 1.—*Sources of Lead in a Child's Environment**

Food
Mixed diet—mean 9.43 μg/kg/d (range 53-132 μg/d)
Bottled baby food—mean 35 μg/liter
Human milk—6-59 μg/liter
Contaminated Sources
Tinned baby foods—mean 202 μg/liter
Cold drink in glazed pottery mug—2,000 μg/liter
Bone meal (health food)—60-190 μg/gram
Paint chips—may contain as much as 100,000 μg/gram
Water
Standards: World Health Organization —<100 μg/liter
Public Health Service (USA) —< 50 μg/liter
Contaminated Sources
Up to 1,850 μg/liter
2,595 samples—1.4% >50 μg/liter, maximum 640 μg/liter
Air
Usual lead content—1-2 $\mu g/m^3$
Contaminated Sources
Smelter A, within 1.6 km— 8-10 $\mu g/m^3$
Smelter B, within 4.0 km—14-16 $\mu g/m^3$
Soil
Remote areas—2-200 μg/gram
Contaminated Sources
Within 1.6 km of smelter—mean 7,600 μg/gram
Urban residential—9-7,890 μg/gram, mean 585 μg/gram
City parks—194-3,357 μg/gram
House Dust
New inner-city homes—2-24 $\mu g/ft^2$ floor surface
Contaminated Sources
Old inner-city homes—33-486 $\mu g/ft^2$ floor surface; mean 11,000 μg/gram[2]
Homes of lead smelter workers—mean 2,687 μg/gram
Homes within 1.6 km of smelter—mean 22,191 μg/gram
Homes located 1.7-3.2 km from smelter—mean 2,124 μg/gram

*Adapted from Chisolm and Barltrop.[8]

*Professor of Pediatrics, UCSD Medical Center.

supply in that the cistern contained 153 μg per dl of lead, and water from the rain barrel contained 1,080 μg per dl. The standard for safe lead levels in water proposed by the World Health Organization is less than 100 μg per liter and that recommended by the US Public Health Service is less than 50 μg per liter. Investigators who visited the home did look for lead-glazed pottery because it is commonly found in Mexico, and cola drinks or fruit juices are excellent vehicles for the dissolving out of the lead from such containers. The usual lead content of air is about 0.5 to 1.0 μg per m^3 and accounts for absorption of about 0.5 μg. It is higher in smog-contaminated areas. In a study in 1976 it was reported that within 1.6 km of a lead smelter stack in Idaho, the air contained 10 to 17 μg per m^3, and 99% of the children younger than 5 years in that radius had toxic lead concentrations in the blood.[9] In 20% of preschool children, the concentrations were above 80 μg per dl, which put them at risk for encephalopathy. In addition to the lead in inhaled air, dust was a larger factor because it is not only inhaled but reaches the mouths of smaller children through hands contaminated with dust and dirt. Soil samples had a lead content of 7,600 μg per gram.

In the second patient and in the third patient recently treated at the UCSD Medical Center, the intoxication was due to the use of a home remedy containing lead. The clinical signs of lead poisoning are vague and the physical findings nonspecific, so a high index of suspicion is required. As these cases indicate, a solid, careful history that includes discussion of remedies that have been used can be very useful in pointing to the diagnosis. In Mexican and Mexican-American patients, the possibility of lead ingestion from this source must be kept in mind.

Toxic Concentrations of Lead

It is of interest to consider the concentration in the blood at which lead is actually toxic. It is probably toxic at any concentration. In experiments on rats, sustained blood lead levels of 10 μg per dl produced renal lesions. The Centers for Disease Control recently have defined a concentration of lead of 24 μg per dl in whole blood as the upper limit of normal for humans. They also have developed a risk classification for asymptomatic children (Table 2),[10,11] which is based on the concentrations of lead and the FEP in the blood. The children in class I are at low risk. Patients in class Ia, in whom the FEP value is elevated but the lead content normal, would be expected to have iron deficiency or erythropoietic protoporphyria. In cases of iron deficiency anemia, the FEP value ranges from 50 to 250 μg per dl. Patients in class Ib, in whom there is an elevated content of lead along with a normal FEP value, usually have a problem with lead that is receding. In class II are children at moderate risk who should be removed from the source of intoxication and rechecked every three months for at least a year. Those in class III are at high risk. They may need further studies concerning lead burden before chelation therapy. Children in class IV and those in class III in whom there are symptoms consistent with lead poisoning are at urgent risk and require chelation therapy.

TABLE 2.—*Risk Classification for Asymptomatic Children**†

Blood Lead Content μg/dl	Free Erythrocyte Protoporphyrin (μg/dl)			
	<34	*35-109*	*110-249*	*>250*
<24	I	Ia	Ia	EPP
25-49	Ib	II	III	III
50-69	‡	III	III	IV
>70	‡	‡	IV	IV

EPP = erythropoietic protoporphyria

*Adapted from "A Statement by the Center for Disease Control."[10]

†Classes I through IV represent increasing degrees of risk or morbidity and are discussed in the text.

‡Combination of results not generally observed in practice; if observed, retest with venous blood specimen immediately

The pathogenesis of lead poisoning begins usually with the ingestion of lead and its absorption from the gastrointestinal tract. Thereafter the lead enters the liver where some is excreted in the bile and the rest enters the systemic circulation. It is deposited chiefly in bone. A lesser amount goes to the soft tissues, such as the erythrocytes, liver, pancreas, kidney and brain. In bone, the content of lead may be six to ten times that in soft tissues.

In bone, lead is handled like calcium; it is deposited as the tertiary phosphate. Factors that favor the deposition of calcium or its release affect lead similarly. Thus, acidosis leads to the mobilization of lead from the bones and may elevate circulating levels of lead, causing symptoms. At the epiphyseal zone, lead produces damage to the osteoid; it is this process that increases density and eventually accounts for the lead lines seen on roentgenographic examination of the bones. The line is not due to the lead itself.

In the soft tissues, lead is a potent inhibitor of enzymes. It has a special affinity for mitochondrial membranes. Erythrocytes have the advantage of ready availability and serve not only the quantitative assessment of the amount of lead in the body but also the functional measurement of clinical toxicity. The FEP test is the most commonly used and is rapidly and easily carried out. Lead blocks two steps in the synthesis of heme (Table 3).[4] The first step inhibited is the conversion of δ-aminolevulinic acid to porphobilinogen; the second is the addition of iron to protoporphyrin. It is this second block that accounts for the increase in free erythrocyte protoporphyrin that forms the basis of the FEP test for the screening of persons for lead poisoning.

In the kidney, lead produces a characteristic lesion in the proximal tubule and the loop of Henle. On microscopic examination there are round, refractile, acidophilic intranuclear inclusions. Clinically, there is a Fanconi syndrome in which there is proteinuria, glycosuria, phosphaturia and general aminoaciduria. Our third patient had proteinuria and glycosuria, and initially it was thought that his disorder was primarily renal. In lead poisoning, the renal lesion is usually reversible.

Involvement of the brain is the most critical element in the intoxication caused by lead from the point of view of both survival and sequelae. Encephalopathy is the usual manifestation in childhood; in adults it is peripheral neuropathy. It is of interest that similar findings are seen in experimental animals. In rat pups, lead enters the mitochondria of the brain where it inhibits respiratory enzymes. In adult rats, lead does not pass the blood-brain barrier. In children, lead entering cortical cells of the brain disrupts mitochondrial function and is responsible for the encephalopathy, which is manifested clinically by seizures and coma. Coma may be seen in the absence of cerebral edema. Edema occurs late, aggravates the situation and becomes life threatening. At necropsy, the brain usually shows intense edema, widespread vascular damage

and degenerative changes. Children with blood lead concentrations in the range of more than 70 μg per dl are at high risk. The first patient, who had coma and seizures, had a blood lead concentration of only 62 μg per dl.

The impact on the developing brain of low levels of lead in the blood is hard to assess. A number of studies suggest that asymptomatic children who have blood lead concentrations in a range of 20 to 40 μg per dl may suffer intellectual and psychosocial impairment. In one study in which school performance and the lead content of deciduous teeth were assessed, a high content of lead was correlated with a decrease in the intelligence quotient of 2 to 4 points, less competence in areas of verbal and auditory processing and decreased attention span.[12] Similar findings have been reported in children living in proximity to lead smelters.[9] Children with higher lead contents were also more likely to have had pica.

Therapy for Lead Poisoning

The therapy for lead poisoning with involvement of the brain and its severity are the critical issues. In patients presenting with encephalopathy such as the first patient, the single most important element of therapy is the removal of lead from brain cells. Before the advent of chelation therapy, children presenting with coma or seizures or both had a mortality rate of 65%. The introduction of treatment with dimercaptol reduced mortality to between 25% and 30%. The substitution of calcium sodium salts of EDTA for dimercaptol did not improve mortality statistics, but the combined use of dimercaptol and EDTA reduced mortality to less than 5%.[13]

Dimercaptol is a dithiol chelating agent that is distributed throughout the body water and enters both the brain and the erythrocytes. It is excreted by both liver and kidney. It reverses the inhibition of the enzymes by heavy metals and provides free sulfhydryl groups. Its toxicity is more disturbing than dangerous. It may produce hypertension, sensation of burning of the lips, nausea and abdominal pain. A problem is that its pharmacologic action lasts only four hours, necessitating intramuscular injections every four hours for optimal results. It is contraindicated in the presence of liver failure and deficiency of glucose-6-phosphate dehydrogenase, where it may produce a hemolytic crisis. It should not be administered along with iron. The dosage is 4 mg per kg of body weight given intramuscularly every four hours for three to five days.

EDTA can be given intravenously or intramuscularly at six-hour intervals. It is not metabolized in the body; 95% is excreted in the urine in 24 hours. It is distributed in 90% of body water, but does not enter erythrocytes and diffuses poorly into brain. In fact, in cases of severe encephalopathy, it may worsen the clinical state and increase hematuria and the plasma concentration of aminolevulinic acid in the first 24 to 48 hours. Toxicity affects the proximal renal tubules. It should be administered only after adequate renal output is assured and never in the presence of anuria or severe renal disease. It may produce hypercalcemia. The dosage of EDTA for children is 75 mg per kg a day divided into four doses given intramuscularly. If given intravenously, it may be given slowly over 3 to 4 hours every 12 hours in a total dose of 50 mg per kg.

EDTA will cause a fall in concentrations of lead in the blood of 20% over the first day of treatment. Treatment with dimercaptol and EDTA combined will cause a fall of 50%,

TABLE 3.—*Effects of Lead Poisoning on the Biosynthesis of Heme**

Normal Pathway	*Intermediate Accumulating in Lead Poisoning*
Succinyl-CoA + glycine	
↓	
δ-ALA	Increased in plasma: Normally less than 0.1 μg/ml, but in lead intoxication, 0.2-1.4 μg/ml; in urine, 0.5 mg/dl or more
Pb → Cytosolic δ-ALA dehydratase	Lead inhibits this enzyme, decreased activity is a very sensitive indicator; found at levels of lead in blood of 10 μg/dl
↓	
Porphobilinogen	
↓	
Uroporphyrinogen III	
↓	
Coproporphyrinogen III	Coproporphyrin III excreted in great excess in urine (signifies current activity)
↓	
Protoporphyrinogen IX	
↓	
Protoporphyrin IX	Accumulates in great excess in erythrocytes and accounts for the fluorescence (this is the basis of the FEP test)
Fe	
Pb	
Mitochondrial ferrochelatase	Lead inhibits this enzyme
↓	
Heme	

δ-ALA = δ-aminolevulinic acid, FEP = free erythrocyte protoporphyrin

*Adapted from Spector and Madden.[4]

along with a pronounced increase in the excretion of lead. This approach also has the advantage of not exacerbating the clinical state initially. Combined therapy is not more toxic. The only problem is the number of intramuscular injections required. In the 8-year-old boy who had ingested *greta* and had a blood level of lead of 93 μg per dl and an FEP of 307 μg per dl, dimercaptol was given intramuscularly and EDTA intravenously. In 24 hours his level of lead was 48 μg per dl; in 96 hours it was 24 μg per dl. In the first 24 hours, his urinary excretion of lead was 25.2 mg, more than half of the total eventually excreted. On the third day 6.9 mg was excreted and on the fifth day 2.1 mg. After two weeks, when the lead burden had reequilibrated, his blood level had reached 55 μg per dl. A second course was administered. This time over the first day he excreted 12.5 mg and on the last day only 0.5 mg. At the time of discharge he was totally asymptomatic and his neurologic state and memory were normal.

The first patient who was comatose and had seizures also had cerebral edema. For this reason, she was given a regimen of mannitol and thiopental sodium in addition to chelation. In our experience, cerebral edema responds well to the administration of mannitol and the removal of lead from the brain cells. It is rarely necessary to be more aggressive. In children who are symptomatic and in those who are asymptomatic but who have a blood concentration of lead greater than 70 μg per dl, we used combined chelation therapy. In the group in whom the level is between 50 and 70 μg per dl, a provocative one-day EDTA test is done to determine the burden of lead. If the amount of lead excreted in the urine is greater than 0.5 mg, a five-day course of EDTA is given. In the group in whom the level is between 30 and 50 μg per dl, removing the child from the source or vice versa may be all that is necessary. All children who are found to be at risk need prolonged careful follow-up. Penicillamine is not a very effective chelating agent for lead and does not have approval from the FDA. It is dangerous to use if a patient is not removed from the source, because it enhances absorption of lead from the intestinal tract.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *How do you make a diagnosis of lead poisoning?*

DR SPECTOR: The definitive diagnosis is based on the concentration of lead in the blood. The FEP test, which is used for screening for lead poisoning, is also positive in cases of iron deficiency anemia (50 to 250 μg per dl). The most sensitive index of lead effect on heme synthesis is the assay of δ-aminolevulinic acid dehydratase. At blood lead concentrations of 30 μg per dl, its activity is reduced 50%.

PHYSICIAN IN THE AUDIENCE: *What is the significance of lead lines?*

DR SPECTOR: The presence of lead lines in the long bones is an index of a heavy lead burden. This can be determined by the EDTA provocative test. Lead is stored chiefly in bone and it is inactive there.

PHYSICIAN IN THE AUDIENCE: *Is anemia always present in patients with lead poisoning?*

DR SPECTOR: Iron deficiency anemia is not due to lead intoxication although it is often seen as an associated finding. Lead itself does not produce significant anemia but is responsible for the basophilic stippling.

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Medical Staff Conference

Na^+-H^+ Exchange, Oncogenes and Growth Regulation in Normal and Tumor Cells

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and formerly Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

LLOYD H. SMITH, Jr, MD:* *For this Medical Staff Conference, we have a most unusual topic. Dr Harlan Ives is a member of the Nephrology Division at Moffitt Hospital, so we are not surprised to find him speaking on the exchange of sodium and hydrogen ions. It is less common for a nephrologist, or anyone else, to move from that topic to a consideration of oncogenesis and growth regulation. Dr Ives, can you really make that transition? We look forward to hearing a review of the work in that area.*

HARLAN E. IVES, MD, PhD:† In the year 1985 we find ourselves in the midst of a revolution in the understanding of carcinogenesis. Fundamental biologic information on the causes of cancerous transformation of cells that could not have been imagined five years ago is now appearing on an almost daily basis in the various journals of medicine, cell biology, biochemistry, virology and even in general medical texts[1] and the popular literature.[2-4] Perhaps even more significant than the quantity of this new information is the extent to which a limited number of themes appears to recur in work drawn from very diverse sources. This convergence of information has resulted in a remarkable level of enthusiasm about the future of this exceedingly complex and important problem.

In this Conference, I would like to convey this flavor of enthusiasm and review some of the scientific basis for it. In doing so, I will review the oncogene hypothesis and the broad areas of experimental evidence that support it, the relationship between oncogene products and normal growth factors, the biochemical effects that growth factors have on cells and the role of sodium (Na^+)-hydrogen (H^+) ion exchange and cell alkalinization in the regulation of cell growth. Although the topic of this review covers the work of much scientific research over the past five years, understanding only a tiny percentage of this work is needed to realize its profound importance for the study of cancer in the years to come.

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The Oncogene Hypothesis

In its simplest form, the oncogene hypothesis states the following:

Cancer is caused by an abnormal expression of genes found in normal cells. Under normal conditions these genes (more than 20 have been found so far—Table 1) are probably involved in normal cell growth and cellular differentiation.

The oncogene hypothesis embraces older theories of carcinogenesis that were based on years of observation and epidemiologic work. These older theories include as causes viruses, carcinogens, genetic predisposition to cancer and some combination of the above. What was lacking in these older theories was an understanding of how these various etiologic agents conspire to cause cancer. Without this understanding, it was exceedingly difficult to develop rational therapies or preventive measures aimed at the root cause of the disease.

How is the oncogene hypothesis able to explain the earlier observations and unify the older theories of carcinogenesis? First, the oncogene work has shown that viruses can cause cancer by introducing abnormal forms of oncogenes (viral oncogenes) that are similar to their normal cellular counterparts (cellular oncogenes). This mechanism has been shown in many carcinomas found in avian, murine and simian species. Second, mutations in a cellular oncogene have been shown to cause cancerous transformation. Because carcinogens are believed to work by causing mutations in a cell's DNA, it would appear that carcinogens, such as those found in cigarette smoke, cause cancer by creating mutations in specific genes (oncogenes). Third, genetic predisposition to cancer may be due to the presence within a family of an abnormal copy of one of the oncogenes. Members of this family then might be predisposed to a certain type of cancer. Last, the observation that cancer is a slowly progressive process, requiring several causative factors rather than one, may be explained by the observation that, in some cases, cancerous transformation can be caused by only several oncogene abnormalities rather than by only one.

(Ives HE: Na^+-H^+ exchange, oncogenes and growth regulation in normal and tumor cells—Medical Staff Conference, University of California, San Francisco. West J Med 1985 Sep; 143:365-370)

What is meant by "abnormal expression" of a normal gene? When does something that is normal become abnormal? Work on this concept has led to a number of important findings. First, it is not surprising that if a specific gene is damaged by a carcinogen, or if a damaged copy is introduced by a virus, the gene product might behave abnormally. For example, an altered protein might not recognize the intended cell type or it might avoid repression by inhibitory factors. A second type of abnormal expression occurs when there are too many copies of a gene that is otherwise normal in structure. This leads to overproduction of its normal product. This overproduction could cause a loss in the "fine tuning" of growth regulation and lead to cancerous growth. Finally, chromosomal translocations, which occur frequently in certain cancers, such as Burkitt's lymphoma and chronic myelogenous leukemia, have been shown in a number of cases to translocate oncogenes from inactive sites of transcription to active sites. Such an increase in transcription would also lead to overproduction of the protein product of an oncogene. Thus a number of relatively simple mechanisms can be envisioned whereby a normal gene could become abnormal and dangerous to the organism.

Evidence for a Role of Oncogenes in Causing Cancer

The evidence that oncogenes are involved in causing cancer comes from remarkably diverse sources. In Table 2 is summarized the most important of these lines of evidence. In the paragraphs that follow, I will present examples of each.

The earliest evidence for the oncogene hypothesis was obtained in the study of viruses that cause cancer in birds and rodents. Although most of these viruses do not appear to be involved in human cancer, the oncogene concept ties virally induced cancers together with nonvirally induced cancers in a clear and convincing way. First, transforming retroviruses (these are viruses that contain RNA, can transcribe it into DNA via the enzyme reverse transcriptase and that cause cancer in birds and rodents) often contain oncogenes. As early as 1911, Rous found a filterable agent that could cause sarcoma in chickens.[5] He believed this agent to be a virus, but because it was firmly believed at the time that cancer is not an infectious process, but rather that it arises de novo in each case, Rous's viral hypothesis was ridiculed for many years. By the 1930s and 1940s, however, it was becoming increasingly clear that not only did the Rous virus cause sarcoma in chickens but other viruses were being found that caused cancers in other species. These discoveries ultimately led, in 1965, to a Nobel prize for Rous, 54 years after his initial work. Yet, even at this late date, the entire significance of Rous's finding was not yet fully appreciated. In 1976 a startling discovery was made in the laboratory of Varmus and Bishop at the University of California, San Francisco. They found that the *src* gene (without which Rous virus does not cause sarcoma in chickens) is actually similar to a gene found in all normal chickens[6] and other higher organisms including humans.[7] Thus, the *src* gene appears to be highly conserved across eons of evolutionary time and is not simply a curiosity of chicken sarcoma. Rather, *src* is a biologic entity of considerable general importance. Since this discovery, more than 20 such retroviral genes have been found that are similar to normal vertebrate and human genes (Table 1). These genes are now referred to as the viral oncogenes, and their animal counterparts are referred to as cellular oncogenes.

The second line of evidence that viral oncogenes are involved in causing cancer is almost an aside to the first. Several retroviruses that cause cancer do not contain oncogenes. However, some of these were subsequently found to uniformly insert viral DNA into a cellular oncogene following viral infection. This phenomenon is called insertional mutagenesis because it mimics mutation through insertion of viral genetic material into oncogenes.[8]

The third line of evidence that oncogenes are involved in cancer actually derives from work with a human cancer—a neoplasm of the urinary bladder. It has long been known that DNA derived from cancer cells, when incubated with normal cells in such a way as to allow uptake of the DNA, can frequently cause transformation of the cells into malignant cells. With modern sequencing and cloning techniques, it was possible to identify the precise DNA sequences that were responsible for this transformation. A "transforming principle" was purified that was 50,000 times more potent than whole cell DNA in causing cell transformation. This DNA

TABLE 1.—*The Current List of Oncogenes, Their Viral Sources and Relationship to Human Cancers*

Gene	*Retroviral Source*	*Human Tumor*
src	Chicken sarcoma	. . .
yes	Chicken sarcoma	. . .
fgr	Cat sarcoma	. .
abl	Mouse leukemia	Chronic myelogenous leukemia
fps	Chicken sarcoma	. . .
fes	Cat sarcoma	Acute promyelocytic leukemia
ros	Chicken leukemia	. .
erb-B	Chicken leukemia	. .
fms	Cat sarcoma	. .
mil	Chicken sarcoma	. .
raf	Mouse sarcoma	. .
mos	Mouse sarcoma	. . .
sis	Monkey sarcoma	Osteosarcoma, glioblastoma
Ha-ras	Rat sarcoma	Bladder carcinoma, other carcinoma
Ki-ras	Rat sarcoma	. . .
N-ras	. . .	Carcinomas
fos	Mouse sarcoma	.
myc	Chicken luekemia	Burkitt's lymphoma, carcinomas
myb	Chicken leukemia	Acute lymphocytic leukemia, ovarian adenocarcinoma
B-lym	. .	Lymphoma
ski	Chicken sarcoma	. .
rel	Turkey leukemia	.
erb-A	Chicken leukemia	. . .
ets	Chicken leukemia	. . .

TABLE 2.—*Major Lines of Evidence That Link Oncogenes to Carcinogenesis*

Transforming retroviruses frequently contain genetic material homologous to the oncogenes
Other transforming retroviruses are capable of inserting viral sequences into a cell's oncogenes
Sequences of tumor cell DNA homologous to oncogenes will transform certain normal cells
Many tumor cells overproduce the protein products of oncogenes
Chromosomal translocations in tumor cells contain oncogenes

turned out to be homologous to one of the viral oncogenes, *ras*. Of perhaps even greater interest, *ras* derived from urinary bladder carcinoma differed from normal *ras* by a single amino acid.[9,10] In other words, a point mutation of an oncogene could transform a normal, benign constituent of the cell to a cancer-causing agent.

Human cancers have now also been shown to overproduce the protein products of oncogenes. Human osteosarcoma cells[11] and human glioma cells[12] both secrete large amounts of a protein with significant homology to the product of the oncogene *sis*. The *sis* gene was originally identified as the gene that enables the simian sarcoma virus to cause sarcoma in monkeys. The protein product of this gene was identified and looked for in various human tumors. Indeed, the cells described produce large quantities of this material, again providing powerful suggestive evidence for a role of oncogenes in causing human cancers.

Finally, evidence for an involvement of oncogenes in human cancer has been arrived at by careful analysis of chromosomal translocations in certain human cancer cells. The best known of these is the Philadelphia chromosome, in which part of the short arm of chromosome 22 is exchanged for a fragment of the long arm of chromosome 9. The abnormality has been known to cytologists and oncologists for many years[13] as a marker for chronic myelogenous leukemia for which it has very high specificity and more than 85% sensitivity. With the development of more sophisticated genetic methods, it has become possible to determine specifically which genes are involved in this transfer of DNA. In 1983 it was discovered[14] that the fragment of chromosome 22 involved in the transfer contains the *sis* oncogene and the fragment of chromosome 9 contains the *abl* oncogene (Figure 1). While it is still not known what role this gene transfer has in transforming bone marrow cells to malignant cells, this finding provides provocative evidence for a role of oncogenes in causing chronic myelogenous leukemia.

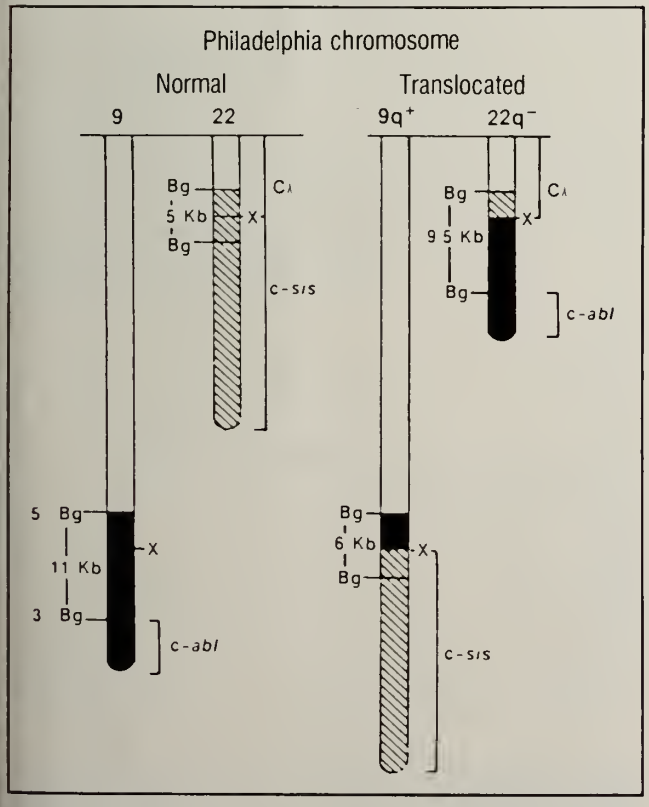

Figure 1.—The fragments of DNA that are exchanged in the Philadelphia chromosome each contain oncogenes (from Heisterkamp et al[14]).

More convincing is the recent finding[15] that chromosomal translocations in Burkitt's lymphoma result in the transfer of the *myc* oncogene from chromosome 8 to the region of chromosome 14 that carries the immunoglobulin heavy chain. This translocation results in the placement of the *myc* gene under new control. Because heavy chains are synthesized in large numbers in these B cells, *myc* synthesis is greatly increased.[16] Although the mechanism by which *myc* transforms the lymphocyte is not yet known, the increase in *myc* product synthesis appears almost certainly to be a crucial factor in this transformation.

The Role of Oncogenes in Normal Cells

If the oncogenes are indeed "normal" genes until they become modified by viruses or carcinogens, then what is their role in normal cells? An answer to this question has begun to emerge from work in many laboratories over the past five years. It appears that some of the oncogene products are involved in the control of normal cell growth and differentiation (for review, see Bishop[8] and Heldin and Westermark[17]). Only when the control of their expression is subverted do they develop the potential to cause cancer. The first hard piece of evidence that this was the case came in 1980. Recall that in 1976, Stehelin and co-workers[7] showed that one of the oncogenes (*src*) was similar to a normal cellular gene. In 1980 it was found that the product for *src* has a most unusual enzymatic activity. The *src* product is a protein kinase that phosphorylates proteins on tyrosine residues.[18] Protein kinases are not at all unusual, but less than 0.1% of the protein-bound phosphate is found on tyrosine residues and no enzyme had previously been described that carried out this phosphorylation. The correlation to growth factors came with a most surprising report from Ushiro and Cohen at Vanderbilt University (Nashville, Tenn).[19] The purified receptor for epidermal growth factor also shows tyrosine-specific protein kinase activity.[19] Subsequently, this enzyme has been found in association with many of the other oncogenes and with the receptors for insulin and platelet-derived growth factor.

More direct evidence for a relationship between oncogenes and normal growth regulation comes from work with cellular growth factors. For many years it has been known that eukaryotic cells do not grow in culture without one of several growth factors found normally in serum. Examples of such growth factors include epidermal, nerve and platelet-derived growth factors and hormones like insulin and vasopressin. In an intact organism, platelet-derived growth factor is responsible for proliferation of cells in the vascular intima after damage. In 1983 Waterfield, Deuel and their collaborators made a remarkable series of discoveries. The oncogene of simian sarcoma virus, *sis*, codes for a protein with a high degree of homology to platelet-derived growth factor[20] and stimulates cells through receptors for the growth factor.[21] Subsequently, Downward and associates, working with Waterfield, found that the product of another oncogene, *erb-B*, has homology with the receptor for epidermal growth fac-

tor.[22] Thus, these oncogene products appear to transform cells through abnormal production of normal growth factors or their receptors. Normally, the production of these proteins is probably only transient, when cell proliferation is required. Cell transformation occurs when growth factor production becomes unregulated.

What Are the Biochemical Effects of Growth Factors on Cells?

Upon binding of a growth factor to a cell surface, a number of significant biochemical events occurs within minutes to hours. The most important of these are summarized in Table 3. Two enzymatic activities appear uniformly to be stimulated upon binding of growth factors. First is the activity associated with the *src* gene, tyrosine-specific protein kinase. As discussed above, tyrosine phosphate is a very rare component of cell protein. Thus, tyrosine-specific protein kinase must work on only a very small number of specific proteins. Thus far, several membrane proteins have been identified that are phosphorylated on tyrosine residues, including the kinase itself, but, other than the kinase activity, the function of these proteins is not known.

A second important biochemical activity stimulated by growth factors is inositol phospholipid turnover. Until recently, inositol phospholipids were thought to be merely a curious minor component of cell membranes. However, it has now become apparent that many growth factors cause enzymatic degradation of inositol phospholipids to inositol trisphosphate and the glycerol backbone, diacylglycerol (for review, see Berridge and Fine).[23] These two breakdown products of inositol phospholipids are probably both intracellular messengers. Inositol trisphosphate appears to have an important role in the mobilization of intracellular calcium (Ca^{++}), and diacylglycerol stimulates the enzyme "kinase C," a calcium- and phospholipid-sensitive protein kinase that phosphorylates a number of proteins on serine or threonine residues.

Third, the interaction of growth factors with cells often causes expression of oncogene products located in the cell nucleus, like *myc* and *fos*. This phenomenon appears to tie together those oncogene products that are similar to growth factors or their receptors with a second set of oncogenes that are expressed after stimulation by growth factors.

The fourth major response of cells to growth factors is an increase in intracellular Ca^{++}. This response does not appear to be specific for growth but rather accompanies hormonal activation of many types.

Last, binding of growth factors to cells causes a rapid increase in intracellular pH from a resting value of about 7.0 to 7.2. Although this increase seems to be small, Daniel and myself (Figure 2) and others[24,25] have had no difficulty in detecting it with modern methods (T. O. Daniel, MD, and H. E. Ives, MD, PhD, unpublished observations, February 1985) and it is certainly large enough to cause profound changes in several important cellular functions.

TABLE 3.—*Biochemical Events Associated With Growth Factor Activation in Many Cells*

Stimulation of tyrosine-specific protein kinase activity
Stimulation of inositol phospholipid turnover
Expression of certain oncogene products
Mobilization of Ca^{++}
Intracellular alkalinization

TABLE 4.—*Some of the Growth Factors That Cause Intracellular Alkalinization*

Platelet-derived growth factor
Nerve growth factor
Epidermal growth factor
Insulin
Thrombin
Concanavalin A
Fertilization (sea urchin eggs)

Growth Factors Cause Intracellular Alkalinization

The idea that cell pH changes might somehow be involved in the process of cell division has been entertained for many years. In fact, as early as 1913, Loeb showed that exposure of sea urchin eggs to ammonium hydroxide could initiate a process of artificial fertilization such that the egg would begin to mature in the absence of sperm.[26] Progress on this provocative idea was not made for the next 60 years because of the difficulty of making accurate cell pH measurements. Not until 1976 did Johnson and associates finally prove convincingly that a 0.3 unit pH change accompanies sea urchin egg fertilization.[27] More important, if this pH change is blocked by low Na^+ or amiloride (an inhibitor of the Na^+-H^+ exchanger), the changes of fertilization do not occur.

What is the relevance of sea urchin eggs to our discussion of growth regulation and transformation in mammalian cells? It now appears that many mammalian cells undergo a similar cell alkalinization as an early response to the presence of growth factors or agents that can cause cancerous transformation of cells. Table 4 provides a partial list of agents that have so far been shown to cause intracellular alkalinization. One of these is platelet-derived growth factor, the protein with significant homology to the transforming protein of the simian

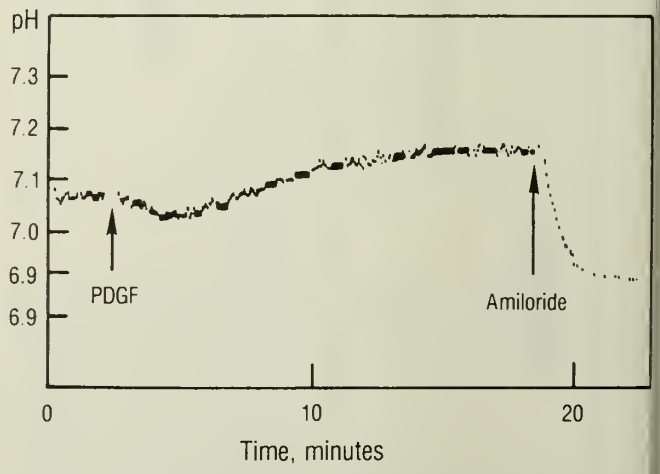

Figure 2.—Measurement of intracellular pH in 3T3 fibroblasts after addition of platelet-derived growth factor (PDGF) and an inhibitor of the sodium-hydrogen ion exchanger, amiloride. pH was monitored with an intracellular trapped fluorescent dye, (2′-7′)-bis(carboxyethyl-[5,6]-carboxyfluorescein).

sarcoma virus, and a protein that is produced in tremendous quantity by human osteosarcoma and glioma cells. It is also of interest that epidermal growth factor, whose receptor is coded for by the oncogene *erb-B*, also causes intracellular alkalinization. How and why do these growth factors and oncogene products cause alkalinization?

How Do Growth Factors Cause Intracellular Alkalinization?

The answer to this question of how growth factors cause intracellular alkalinization requires some knowledge of how cells regulate their pH under ordinary circumstances. Because of the interior negative membrane potential found in most cells, and because of metabolic acid production, cells must constantly extrude H^+ to maintain the normal intracellular pH of 7.0 to 7.2. The mechanism for intracellular pH regulation in higher organisms (in bicarbonate-free medium) is Na^+-H^+ exchange. In bicarbonate-containing media, an additional pH regulatory system has been found in some cells. However, this latter system is beyond the scope of this review. Na^+-H^+ exchange harnesses the energy present in the Na^+ gradient (formed by action of the sodium-potassium adenosine triphosphatase [Figure 3]) to drive H^+ out of the cell. Because Na^+-H^+ exchange never reaches thermodynamic equilibrium, it is possible for a cell to alter its pH by changing the rate at which Na^+-H^+ exchange is operating. Thus, if Na^+-H^+ exchanger activity were increased, the cell pH would rise, and if Na^+-H^+ exchange activity decreased, cell pH would decrease.

Current evidence indicates that this is precisely how growth factors cause an increase in intracellular pH. This evidence can be summarized as follows:

- Alkalinization caused by growth factors is accompanied by Na^+ entry.[24,25,28]
- Alkalinization is blocked by the removal of Na^+ from the medium.[25,28]
- Alkalinization and Na^+ entry are both blocked by the diuretic drug amiloride,[25,28,29] which is known to inhibit the Na^+-H^+ exchanger in isolated membrane systems.[30,31]

Why Do Growth Factors Cause Intracellular Alkalinization?

The answer to the important question of why growth factors cause intracellular alkalinization is not yet completely known. However, work from the laboratory of Pouysségur and co-workers in Nice is beginning to unravel the mystery.[29,32] They cleverly obtained mutants of fibroblasts that lack Na^+-H^+ exchangers. These mutants grow normally at alkaline pH but cannot maintain growth if the pH of the medium is reduced below 7.2. (Wild type cells grow, albeit slowly, even when the pH is reduced to 6.5.) Pouysségur and associates looked at the intracellular pH of both types of cells as extracellular pH was lowered. Wild type cells tend to maintain their intracellular pH near 7.2 even as the medium is reduced below pH 7.0. Cell pH in the mutants could not be maintained as medium pH was lowered. When they looked at the dependence of DNA synthesis on intracellular pH in these cells, they found that DNA synthesis is shut off precisely at pH 7.2 in both types of cell. Thus, it appears that the reason the mutants cannot grow in acid medium is because they cannot maintain their intracellular pH above 7.2 in acid

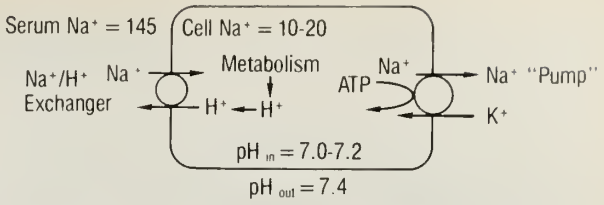

Figure 3.—The cell maintains its intracellular pH by extrusion of hydrogen ion (H^+) in exchange for entrance of sodium ion (Na^+) into the cell. The energy for this transport process comes from the low cell Na^+ that in turn is generated by action of the Na^+-potassium (K^+) adenosine triphosphatase (ATPase).

growth media. Finally, in a separate work,[32] Pouysségur and colleagues showed that amiloride analogues block DNA synthesis in wild type cells with the same order of potency that they block Na^+-H^+ exchange in these cells. Thus, it appears that Na^+-H^+ exchange is necessary for the maintenance of the correct cell pH for DNA synthesis and cell division to occur. Growth factors and certain oncogene products stimulate Na^+-H^+ exchange and thus provide the proper intracellular environment for cell division of cancerous transformation.

These remarkable new findings that I have discussed here seem to provide a firm basis for the understanding of the cause of many, if not all, types of cancer. Thus far these new laboratory findings have not yielded new approaches in the treatment of cancer, but it seems only logical that these will be forthcoming. On this problem, Bishop has said, "Will we be able to parlay the growing information about oncogenes into devices for the prevention, diagnosis and treatment of human cancer? It is too early to foretell how quickly the answer to this question might come, but there now seems little reason to doubt that we have laid hold of cancer with a grip that should eventually extract the deadly secrets of the disease."[1]

Summary

Cancerous transformation of cells is caused by the altered expression of one or more of a small group of genes known as "oncogenes." This altered expression can be due to a mutation of the gene or to a derangement in the rate of production of the product of an otherwise normal gene. Under normal conditions, these genes are almost certainly involved in normal cellular growth and differentiation. In several cases, oncogene products appear to be closely related to growth factors found in normal serum. These growth factors are known to cause a number of biochemical alterations within cells. One of these alterations is intracellular alkalinization, stimulated by increased activity of the Na^+-H^+ exchanger. This alkalinization appears to be necessary for the initiation of DNA synthesis.

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Epitomes
Important Advances in Clinical Medicine

Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in radiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Positron-Emission Tomography of the Heart

MYOCARDIAL PERFORMANCE is determined by complex biochemical processes that modulate contractility, electrophysiologic events and cell viability. In vivo assessment of myocardial metabolism has been difficult to accomplish in the past. Until recently, nuclear cardiologists focused on functional imaging such as the evaluation of myocardial blood flow using thallous chloride Tl 201 and the study of ventricular function by radionuclide ventriculography. With the recent advent of positron-emission tomography (PET), however, the field of nuclear cardiology enters a new era by imaging regional metabolic processes. This tomographic, three-dimensional approach provides quantitative determination of myocardial tracer distribution because photon attenuation can be accurately corrected for. Positron-emitting isotopes such as fluorine 18, oxygen 15, carbon 11 and nitrogen 13 can be used to label physiologically occurring substrates for the in vivo study of myocardial cell function. The current generation of the PET cameras with high spatial (5 to 10 mm) and dynamic resolution (three to ten seconds per image) provide accurate quantitation of myocardial perfusion and metabolism using validated tracer kinetic models. These characteristics make positron-emission tomography a unique tool for the in vivo assay of biochemistry, which links structure and function in a living organism.

In studying the heart, PET has been used mainly in patients with ischemic heart disease and cardiomyopathy. Regional myocardial blood flow is being evaluated using rubidium chloride Rb 82, ammonia N 13 and water O 15, whereas myocardial substrate metabolism is studied using carbon palmitate C 11 as a tracer for fatty acids and fluorine deoxyglucose F 18 (FDG) as an analog for glucose. Using PET, studies in animals and clinical studies have shown that normal myocardium is characterized by a close match of flow and substrate metabolism because both reflect regional energy demand. The same is true for infarcted myocardium where flow and metabolism are low due to the low perfusion and energy requirements of scar tissue. During ischemia, myocardium cannot oxidize fatty acids but uses glucose anaerobically to meet its basic energy requirements. This regional shift in myocardial metabolism during ischemia can be detected noninvasively by PET as shown in experimental and clinical studies. Therefore, ischemic but viable tissue can be detected noninvasively. Using metabolic tissue characterization, studies of animals showed that PET can predict recovery of function following transient ischemia. Encouraged by these results, PET has been applied to patients with acute myocardial infarction. In a considerable number of patients, viable but compromised tissue was observed in "electrocardiographically infarcted" segments of the left ventricle. The metabolic definition of viable but compromised myocardium early during evolving infarction is most important for salvaging myocardium in view of therapeutic interventions such as thrombolysis and angioplasty. Additionally, in patients with severe coronary artery disease and impaired left ventricular function, PET images have been shown to be predictive for the success of a coronary artery bypass procedure. Myocardium with impaired flow but maintained glucose metabolism as estimated by FDG uptake showed functional recovery, while segments with low flow and low metabolism did not recover postoperatively. Because patients with impaired ventricular function have a higher surgical risk, carefully selecting patients for a surgical procedure is clinically important.

In cases of dilated cardiomyopathy, heterogeneous free fatty acid metabolism has been shown by a patchy uptake pattern of carbon palmitate C 11. Furthermore, in patients with severe left ventricular dysfunction, the response of fatty acid metabolism to glucose loading was substantially abnormal. To improve our understanding of the pathophysi-

ology of cardiomyopathy, further research in this area will focus on detecting biochemical defects before deterioration of function occurs. Finally, in patients with Duchenne's muscular dystrophy, there is evidence of a localized myocardial metabolic abnormality that is unique to this disease and can be detected by PET. Again, FDG proved to be a sensitive marker of a regional shift in substrate metabolism.

Positron-emission tomography is still in its infancy, but these initial studies show the potential for metabolic imaging in cardiac disease, especially for such important clinical questions as defining tissue viability in patients with ischemic heart disease. Refining the technique will allow more accurate diagnosis of cardiac disease and better biochemical understanding of the underlying cause.

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New Developments in Contrast Media

RESEARCH OF CONTRAST MATERIAL has recently brought into focus a number of new developments that should have major impacts on the practice of radiology in the near future.

The first of these is the production and clinical testing of low-osmolality media. In general, these new substances take one of two forms: nonionic agents or monoacid dimeric agents. These substances differ from the current ionic media by a decrease in the osmotic pressure of the molecules for a given concentration of iodine. Thus, the new media have a ratio of iodine atom to dissolved particle of 3, whereas current media have a ratio of 1.5. Animal and clinical testing to date indicate that the low-osmolality media are both safer and more comfortable when used for arteriography. While the chemotoxicity of these media is substantially less than that of current media, the data on anaphylactoid effects are still incomplete. Preliminary findings, however, suggest that a significant improvement can be expected in this area also. Currently, only one nonionic agent (metrizamide) is approved for intravascular use in this country. Other nonionic agents are pending approval by the Food and Drug Administration and, when available, will probably become the agents of choice for arteriography. Because they are expected to be considerably more expensive than current ionic media, their overall role in vascular injections remains to be determined. Results of both studies on animals and clinical studies suggest that these media will also confer less toxicity in the subarachnoid space than metrizamide or iophendylate (Pantopaque).

The second development of note concerns the use of perfluorocarbons as contrast agents for ultrasonography. Nonbrominated perfluorocarbons are presently used in humans as oxygen-carrying blood expanders and these substances, when injected as emulsions in both the brominated and nonbrominated forms, appear to combine a low toxicity with effective uptake by reticuloendothelial cells and macrophages, resulting in increased echogenicity of the liver and spleen and experimentally induced tumor rims and myocardial infarcts. Preliminary trials in humans are currently under way and appear highly promising, particularly for enhanced visualization of liver tumors.

The third area of particular interest is the development of contrast agents for magnetic resonance (MR) imaging. Preliminary observations suggest that such agents will dramatically extend the diagnostic value of MR imaging, despite the inherent high-contrast differences obtainable for different tissues with this new technique. Conventional radiographic contrast media produce their effect by high-electron density that absorbs x-rays. MR imaging media, as currently conceived, function by altering local magnetic environments. These paramagnetic substances can be used for intravascular injection, subarachnoid installation or gastrointestinal tract opacification. Data on animals and preliminary data on humans suggest that these compounds can be used effectively in a fashion similar to that of conventional media with very low toxicity anticipated.

Each of these new developments should reach a stage of clinical use within one to three years, with the advent of the new nonionic media for conventional radiography expected within a year.

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Computed Tomography of the Spine

BECAUSE OF ITS ABILITY to show both soft tissue and bone abnormalities in excellent detail, high-resolution computed tomography (CT) has assumed a dominant role in imaging of the spine, particularly in the lumbar area. Its efficacy in evaluating degenerative disc disease, tumor, trauma, congenital abnormalities and infectious processes has been documented.

More than 95% of lumbar disc herniations occur between L-3 and S-1, so that by scanning these three levels most lumbar disc problems will be encompassed. Contiguous 4- to 5-mm thick axial scans are taken, with additional scans parallel to the discs obtained in some cases. Contiguous scans decrease the likelihood of missing herniated disc fragments that have migrated above or below the disc level and, in addition, make possible sagittal and coronal reformations that are useful in some cases. CT is more accurate than conventional myelography in diagnosing lumbar disc herniation because even lateral and L5-S1 herniations remote from the thecal sac can be readily seen. CT clearly shows central and foraminal spinal stenosis that often plays a significant role in low back syndromes. Abnormalities of the facet joints, which may contribute to low back pain, are also clearly shown. By showing whether root compression is due to focal herniation or bulging of the annulus and whether there is extruded disc material, selection of appropriate therapy such as surgical repair or enzyme injection can be aided. Evaluating the lumbar spine postoperatively with plain CT may be difficult because of surgical distortion. The use of intravenous contrast media in this situation can help distinguish between recurrent disc herniation and scarring.

The role of plain CT in evaluating cervical disc disease is more controversial. Although thin-section CT (1.5- to 2-mm slices) can demonstrate disc herniations and spondylotic changes, diagnostic accuracy is not as high as in the lumbosacral spine. Many authors advise using an intrathecal water-soluble contrast agent to improve the diagnostic accuracy of CT examination of a patient with cervical degenerative disc disease.

The major limitation of plain CT is its inability to show intradural pathologic processes such as tumors. Conventional myelography or CT with intrathecal water-soluble contrast material is indicated when an intradural abnormality is suspected.

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Radiation Risks in Diagnostic Radiology

THE RISKS OF HARMFUL GENETIC and somatic effects associated with the low doses (a few rads or less) of ionizing radiation received during diagnostic x-ray examinations are too small to be measured. The existence of deleterious effects from much higher doses is irrefutable. The major uncertainty in inferring low-dose risks from dose-effect data obtained at high doses is selecting the type of extrapolation to be used in continuing the dose-effect curve into the low-dose region. Estimates obtained from a no-threshold, straight-line extrapolation of high-dose dose-effect data in animals and, in some instances, humans, to low doses, will be used here. Such estimates are generally considered "worst case," in that alternative plausible extrapolation schemes lead to lower estimates of risk at low doses.

The genetic risk resides in radiation-induced mutations, generally considered deleterious, which can be passed on to future generations via reproduction. No deleterious genetic (or somatic) effect has ever been documented from natural background radiation. This suggests that if the genetically significant dose, estimated in 1970 to be 0.02 rad per capita per year, remains well below the background radiation dose of 0.1 rad per capita per year at sea level, any additional genetic consequences will neither differ in kind nor exceed in quantity those that have been experienced throughout human history. To obtain a numerical estimate is futile, but taking into account that the dose required to double the spontaneous mutation rate is generally assumed to be 20 to 200 rads, the genetic risk of ionizing radiation from diagnostic x-ray studies would appear to be small. Even so, prudence dictates the maximum possible reduction of human gonadal exposure from diagnostic x-ray studies. To this end, gonadal shielding should be used whenever possible during x-ray procedures on a potentially procreative person.

No direct evidence exists for an association between radiation exposure in utero and harm to an unborn child as a result of a diagnostic x-ray study of the lower abdomen or pelvis of a pregnant woman. However, indirect evidence suggests the possibility of radiogenic birth defects and childhood leukemia. The estimated hypothetical risk of an observable birth defect from a 1-rad in utero dose is 1 to 5 chances in 1,000, whereas the natural incidence rate of birth defects is 40 to 50 per 1,000 live births. Studies in animals indicate that the most critical period for inducing a deformity is during organogenesis, weeks 3 through 7 postconception in humans. Human in utero exposure at high doses from the atomic bomb explosions at Hiroshima and Nagasaki indicates weeks 8 through 15 postconception to be the most critical period for inducing mental retardation. Although not seen in these persons, an increased chance of childhood leukemia for an in utero dose of 1 to 2 rads, from a spontaneous incidence rate of 1 per 3,000 to 1 per 2,000, is suggested by some retrospective epidemiologic studies. These possible risks should be explained to a pregnant patient and documented in her record.

The major concern regarding postnatal exposure to diagnostic x-ray studies is carcinogenesis. The estimated hypothetical lifetime risk per study of cancer developing after a latent period of 10 to 25 years varies from a few chances in a million for a (0.05-rad) two-view chest examination to almost 100 chances in a million for a (3-rad) computed tomographic brain scan. These risks are modest compared with the lifetime risk of dying in an auto accident—1 in 100—or contracting cancer spontaneously—180 in 1,000. The most recent screen-film systems for mammography deliver a mean glandular tissue dose as low as 0.1 rad for a two-breast, two-view study, giving an estimated lifetime risk per study for breast cancer induction after a latent period of 10 to 25 years in a woman aged 40 years or older of no more than a few chances in a million, compared with a natural risk of 1 in 10. The hypothetical risk is down dramatically from a decade ago as a result of the great reduction in dose which fact supports routine screening by age 40 as suggested by the American College of Radiology and the American Cancer Society.

In conclusion, the risks from diagnostic x-ray studies are too small to be measured directly. Estimates of the hypothetical risks show them to be small compared with many risks encountered in day-to-day life in American society. Nonetheless, diagnostic x-radiation must be used prudently and every attempt made to obtain the desired diagnostic information with the minimum radiation dose.

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Neonatal Intracranial Ultrasonography

ULTRASONOGRAPHY OF THE NEONATAL BRAIN is a quick, noninvasive procedure that can be done on fragile neonates in an intensive care nursery without sedation. High-frequency sector-image ultrasound is used to examine the brain through open fontanelles and sutures.

Ultrasonography is most important for diagnosing intracranial hemorrhage due to the combination of immaturity of the germinal matrix that lines the ventricles and immaturity of the lungs and the autoregulatory system. This bleeding is the

most common central nervous system (CNS) disorder in premature infants younger than 32 weeks' gestation, occurring in 40% to 60% of such children. Ultrasonography can show subependymal, intraventricular or intracerebral germinal matrix hemorrhage in the acute or the convalescent phase.

Serial examinations are helpful for evaluating the progression of hemorrhage, the development and course of posthemorrhagic hydrocephalus and, in some cases, the development of periventricular leukomalacia or porencephaly. Ultrasonography of periventricular leukomalacia is now considered more accurate and reliable than computed tomography (CT).

Ultrasonography can be helpful in diagnosing CNS malformations such as congenital hydrocephalus, holoprosencephaly, agenesis of the corpus callosum, hydranencephaly, Dandy-Walker cysts, intracerebral tumors and arteriovenous malformations. CT, angiography or both may be necessary for further characterization.

Ultrasonography is also useful in evaluating term neonatal asphyxia, intrauterine and postnatal CNS infections, head trauma and hemorrhage due to coagulopathy, but CT is usually more definitive in such cases. Cerebellar and subarachnoid hemorrhage is difficult to image with ultrasonography because the cerebellum, the subarachnoid space and clotted blood are all echogenic.

Because the anterior fontanelle is the primary window used to examine the brain, a small fontanelle or overlapping skull bones will limit the quality of the examination. Also, the convexities of the cerebral spaces are not adequately visualized from the anterior fontanelle and, therefore, CT is preferable for examining these areas. Subcutaneous emphysema will also limit or preclude ultrasonography of the brain.

Ultrasonography has proved useful for diagnosing and following various neonatal brain disorders. And it can be used on infants whose condition is too unstable for them to be examined by other methods.

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Percutaneous Removal of Renal and Ureteral Stones

PERCUTANEOUS REMOVAL of symptomatic renal and ureteral calculi is now a routine radiologic method that has replaced open stone operations in the vast majority of patients. Not only simple renal pelvic stones but also calyceal, ureteral and staghorn calculi can be managed successfully percutaneously.

Assessing a patient's blood coagulating properties and obtaining informed consent are part of the routine preprocedure workup. Pretreating with antibiotics is important in patients with a history or symptoms of urinary tract infection. Carefully evaluating the patient's renal anatomy based on previously taken intravenous urograms is essential for planning the optimal access route. We do dilations up to 24 or larger French sizes as a single-step procedure using epidural anesthesia. With the aid of fluoroscopy or endoscopy, stones are removed using baskets, grasping forceps or by ultrasonic lithotripsy. A nephrostomy tube is left in the renal pelvis for at least 24 to 48 hours. It is removed when residual stone fragments have been excluded and good antegrade flow of urine has been confirmed. Hospital stays range from three to seven days in uncomplicated cases, but may be as long as two to three weeks in patients with staghorn calculi or many calyceal stones. Close cooperation between the radiologist and urologist has proved helpful for optimal patient management.

The success rate for percutaneous removal of kidney stones is 95% and for removal of ureteral stones it is about 90%. Occasional stone fragments left behind are usually small and asymptomatic.

Major complications occur in less than 5% of patients. They include hemorrhage, which is usually well controlled by blood transfusions and balloon tamponade and rarely requires angiographic embolization. A surgical procedure and nephrectomy are extremely rare complications. Urosepsis occurs in less than 1% of patients and responds readily to antibiotic treatment, provided there is good urinary drainage.

The advantages of percutaneous stone removal over surgical nephrolithotomy or ureterolithotomy are lower morbidity, shorter hospital stay, shorter recovery period and reduced cost.

A new technique for renal stone removal is extracorporeal shock wave lithotripsy. This is a noninvasive method that uses focused ultrasound waves to fragment stones. Its overall success rate approaches 90%. Percutaneous nephrostomy with tract dilatation is the method of choice in the other 10% of patients. Furthermore, percutaneous or retrograde manipulations of the genitourinary tract are required in 8% or 9% of patients who are treated with this technique to relieve ureteral obstruction resulting from passing stone fragments.

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Ultrasonography in the Operating Room

RECENT TECHNICAL ADVANCES in instrumentation have led to diverse and innovative applications of ultrasonography including its use in the operating room. High-resolution real-time ultrasound units that are portable with scan heads that are relatively small and easily maneuvered have greatly increased the number of uses of sonography in the operating room. The ultrasound probes are placed directly onto the operative field after the probe is enclosed in sterile coverings. In this way, real-time imaging of the operative site provides a surgeon with immediate information before, during or after the operation.

One of the original and now well-established uses of intraoperative ultrasound is in the neurosurgical suite. There are three main applications of intraoperative ultrasonography in neurosurgery: guiding a shunt tube placement, brain biopsy and spinal cord operations. Sonographic monitoring of shunt tube placement allows correct positioning and alleviates pos-

sible complications associated with tube placement. Ultrasonography can guide a neurosurgeon in locating a tumor for possible resection and it may be used to evaluate the adequacy of resection after the procedure. In cases in which either an intracerebral or an intraspinal biopsy without resection is necessitated, specialized biopsy guide attachments may be used to allow visualization of the biopsy needle as it is passed into a lesion. Closed brain biopsy improves the rate of tissue recovery and decreases the time of operation. Recently, intraoperative ultrasonography has also been helpful in monitoring the reduction of spinal fractures.

Neurosurgical applications of high resolution intraoperative ultrasonography have been adapted recently for other areas of the body. The development of small high-resolution probes allows their use within the abdomen. The use of ultrasonography to examine the biliary tract and pancreas during a surgical procedure has received the greatest attention. Some of these applications include assessing the gallbladder and biliary system for calculi, locating the common bile duct during difficult explorations, assessing the extent of pancreatitis and detecting and evaluating pancreatic neoplasms. When renal stone resection is required, ultrasonography may be used for guidance. It will show the site of renal calculi and aid a surgeon in avoiding vital structures such as renal arteries and veins during dissection. Sonography has been helpful in detecting intra-abdominal abscesses or in guidance for resection of intra-abdominal tumors. Precision in localization in the abdomen with ultrasound has dramatically reduced the need for extensive surgical exploration, thus avoiding possible complications in critical areas, and it is helpful in assessing the adequacy of a surgical procedure.

Another possible application of intraoperative ultrasonography is in vascular operations to precisely locate pathology before a vessel is open and to check for vascular defects after reconstruction is completed. Ultrasonography can be used in small vessels including during intraoperative assessment of aortocoronary bypass grafts. There are a large number of current and future applications of intraoperative ultrasonography. The acceptance of a particular use will depend on the practical value of ultrasound to reduce operating room time, increase operative safety and ensure the success and efficiency of surgical procedures by improving diagnosis and localization.

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Mammography—Its Use and Risks

MODERN MAMMOGRAPHY is the most accurate method known for evaluating the breasts. It is capable of detecting breast cancer at an earlier, highly curable stage.

Mammography is indicated in a woman who has a breast mass, pain or nipple discharge. It is useful not only in evaluating the site of clinical abnormality but also in surveying the opposite breast. In patients with metastatic disease of unknown origin, mammography is indicated in the search for a primary lesion.

Mammography is the only examination regularly capable of detecting "minimal cancers," those that are in situ or infiltrating but less than 5 mm in diameter. It is the only imaging method currently acceptable for screening asymptomatic women. The American Cancer Society recommends that every woman have a baseline mammogram between the ages of 35 and 40. Subsequent examinations should be obtained every one to two years, depending on risk factors. At age 50 and older, yearly mammography is recommended.

Although mammography represents the "gold standard" in breast imaging, its limitations should be recognized. First, the accuracy of mammography is limited in women with radiographically dense breasts. A false-negative rate as high as 10% may occur in cases of clinically palpable carcinoma, particularly when the breasts are very dense. If there are clinically suspicious palpable findings, then the lack of specific findings on mammography should not preclude further investigation, including needle aspiration or biopsy. Second, mammography does not always give a specific diagnosis—that is, it may detect a mass but additional procedures, such as ultrasonography to determine if the mass is solid or cystic, and aspiration or biopsy may be necessary to determine whether the mass is benign or malignant. Third, because the breasts of women in their teens and twenties tend to be dense, and because the breast parenchyma is felt to be more sensitive to the effects of irradiation in these patients, mammography should be restricted to cases in which there is a high clinical index of suspicion of malignancy. If there are clinically palpable masses in young women, ultrasound should be considered for the initial examination. If an ultrasonogram does not adequately answer the clinical questions, then mammography should be used.

The radiation doses in mammography are quite low, particularly the doses for screen-film mammography. Based on figures from the Breast Cancer Detection Demonstration Projects carried out throughout the United States in the 1970s and early 1980s, the average breast doses for two-exposure examinations are 0.08 rads for screen-film technique and 0.74 rads for xeroradiographic technique. Because film-screen mammography and xeroradiographic mammography are considered to have similar accuracy, there has been increasing consumer interest in film-screen mammography with its lower dose.

The radiation doses and risks should be taken in perspective. Assuming the maximum acceptable dose of 1 rad for a two-view examination, the theoretical risk of a radiation-induced breast carcinoma is 3.5 cancers per million women per year per rad. In contrast, the natural incidence of breast carcinoma ranges from 800 cases per million women per year at age 40 to 2,500 cases per million women per year at age 65. The theoretical risks of mammography are comparable to those of everyday activities such as driving a car.

Mammography is an extremely accurate and safe method for evaluating the breasts of symptomatic women older than 30 and asymptomatic women older than 35. The benefit-risk ratio of mammography is highly favorable and, it is hoped,

will continue to improve as additional technologic innovations result in superior images with lower doses.

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Noninvasive Doppler Ultrasonography of Carotid Arteries

THE DEVELOPMENT of Doppler ultrasound has greatly enhanced our ability to diagnose a variety of arterial and venous diseases. To date, one of the primary indications for the use of Doppler ultrasound is in investigating cases of possible extracranial carotid artery occlusive disease. This is often referred to as carotid duplex scanning, which is a combination of high-resolution real-time imaging of the carotid arteries with pulsed Doppler wave form and spectral analysis.

In general, patients with a clear-cut history of transient ischemic attacks or reversible ischemic neurologic deficits are studied primarily with selective carotid angiography. Carotid duplex scanning is generally reserved for screening patients who have either an asymptomatic carotid bruit or an unclear history of a transient ischemic attack. In direct comparison studies with selective angiography, carotid duplex scanning has proved to be a reliable technique in showing significant atherosclerotic stenoses at the carotid bifurcation, with accuracies ranging from approximately 85% to 95%. In fact, some authors claim an increased sensitivity for carotid duplex scanning by its ability to detect relatively small plaques that may go undetected by a study such as angiography, which merely shows intraluminal anatomy rather than direct mural lesions.

Specific Doppler criteria for estimating the extent of stenosis have been established by several authors using either a ratio of maximal peak systolic internal carotid flow velocity to maximal common carotid peak systolic flow velocity or using the overall quantitative peak frequency shift obtained within the internal carotid. In persons with normal anatomy, there are both characteristic sounds and wave forms of the internal carotid, external carotid and common carotid arteries. One of the great advantages of carotid duplex scanning is that it combines both anatomic information by virtue of high-resolution real time with the ability to diagnose physiologic disturbances and blood flow with pulsed wave form Doppler analysis. Approximately 10% of carotid bifurcations cannot be adequately imaged with carotid duplex scanning because of a high cervical location of the bifurcation.

One of the major limitations of carotid duplex scanning is that it is operator-dependent. It requires significant experience and commitment to mastering this technique to achieve good results. In experienced hands, however, it is a relatively rapid, noninvasive and inexpensive method of evaluating the carotid bifurcation for significant atheromatous stenoses. To date, the sensitivity for carotid duplex scanning in diagnosing ulcerations is not known, however, because of the inherent tomographic nature of this technique; partial voluming of an irregularly surfaced plaque may lead to misdiagnosis. Because of the ability of carotid duplex scanning to directly image a plaque, in some instances it is possible to characterize the histologic features of a plaque by its sonographic appearance. Calcified plaques produce areas of high-amplitude echoes with acoustic shadowing. Intraplaque hemorrhage has received a great deal of interest in the surgical literature and may be responsible for significant neurologic symptoms, as platelet-aggregate emboli may ensue. Early reports suggest that carotid duplex scanning may have a role in the diagnosis of intraplaque hemorrhage, indicating a biologically unstable plaque even in the absence of a hemodynamically significant stenosis.

When compared with other less invasive techniques such as intravenous digital subtraction angiography, carotid duplex scanning has a number of distinct advantages. First, it is not dependent on patient motion or cardiac output. Second, it is completely noninvasive and does not involve intravenous administration of any contrast media. Third, it is significantly less expensive and often less time consuming. In summary, carotid duplex scanning has proved to be a reliable and clinically useful technique in experienced hands in evaluating significant carotid bifurcation disease.

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Magnetic Resonance Imaging

EXPERIENCE WITH the use of magnetic resonance (MR) imaging for clinical diagnosis has been ongoing for more than three years at several centers in the United States and in Great Britain. It is now clear that MR imaging will assume an important place in clinical diagnosis and biomedical research. It has the following distinct advantages: soft tissue contrast resolution far exceeding the limits of computed tomography (CT) and ultrasonography, absence of possible mutagenic effects inherent with ionizing radiation, unequivocal blood pool identification without the need for contrast media and direct imaging in multiple planes (coronal, sagittal, transverse).

These diagnostic advantages have already been recognized for imaging of four parts of the body. MR imaging is the procedure of choice for most purposes in evaluating the central nervous system (CNS), including the spinal cord. Among its advantages are definitively diagnosing leukoencephalopathies such as multiple sclerosis, greater sensitivity for defining brain lesions compared with using CT, improved depiction of lesions in the posterior fossa through sagittal images and freedom from bony artifacts and visualizing the spinal cord without contrast media and discriminating various pathologies within the cord itself.

The natural contrast between the blood pool and cardiovascular structures makes it valuable for cardiovascular imaging. Recent studies have shown its accuracy for the completely noninvasive evaluation of aortic aneurysms and dissections; tumor and bland thrombi within cardiac cham-

bers, arteries and veins; intracardiac and paracardiac masses; presence, site and complications of myocardial infarctions; constrictive pericarditis; hypertrophic cardiomyopathies, and congenital heart disease. Recent reports have indicated its capability for directly visualizing acutely infarcted myocardium and differentiating infarcted from normal myocardial tissue.

High-contrast resolution and multiplanar image acquisition make MR imaging an important modality for imaging of the pelvis, including the diagnosis and staging of prostate, bladder and gynecologic tumors. The sharp discrimination of endometrial and myometrial layers provides the capability to evaluate focal, small tumors and to assess response to oncotherapy and hormonal interventions. Accuracy for the early diagnosis of renal transplant rejection has been shown.

Musculoskeletal applications are now becoming evident: early identification of avascular necrosis, the medullary extent of bone tumors and lumbosacral disc disease. The recent introduction of thinner tomograms (2.5 mm) extends the uses of MR imaging for evaluating disc disease.

The enormous potential of MR imaging has been clearly evident in the first years of clinical operation. The future role is probably underestimated, however, since MR imaging is being compared with other modalities at a time when it is still an immature and rapidly evolving technology.

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Editorials

How Can Organized Medicine Ever Do All the Things It Ought to Do?

EVERYONE HAS IDEAS about what the medical profession and organized medicine ought to be doing at this perplexing moment in the history of health care in this nation. Some might want to declare victory and say that all of today's health care problems are simply the problems of success of a system that brought better health care to more people than at any other time in history. This is true, but it doesn't solve many of the problems we have today. The clock moves forward, and it is the side effects and complications of this unprecedented medical and social achievement that are becoming evident, and with which both medicine and society must try to learn to cope. It is also becoming clear that many of the things that have to be dealt with are all going on at once. None of them can be ignored for long except at some peril. The intensity of these concurrent urgencies seems to be something new. Our accustomed way of doing things, which is to apply our energies and resources to what seem to be the highest priorities at a given moment, is inadequate to deal effectively with this new problem of so many high priority concerns that all need to be dealt with at the same time.

Almost every physician and just about every medical society knows what these concerns are. Each seems to take the form of a crisis, and each new crisis seems to pile on top of all the others before any of them are really solved. We have a malpractice crisis; we have never-ending legislative crises; problems in financing the cost of patient care and medical education; a host of governmental and third party interventions in health care; ethical problems and adversary relationships developing between hospitals and physicians as a result of the element of competition that has recently been introduced into health care, and more recently what appears to be a lessening public approval of the performance of the medical profession as a whole, although a person's own physician still seems to be held in relatively high esteem. And even these are only some of the more pressing problems facing the medical profession. All in all, it is little wonder that physicians are turning to their medical associations for guidance—and solutions. The physician membership in organized medicine may ask if the medical profession can ever hope to deal effectively with all these concurrent problems. Will it ever be possible to do all the things the profession ought to do? It just may be that frustration about this, as well as the ever increasing cost of membership in medical associations, may contribute to the slippages in membership retention that many associations are beginning to experience.

But need this be so? How might organized medicine begin to deal more effectively with all these concurrent and complex problems that are the side effects and complications resulting from a superb medical and social achievement? A good start has been made. The medical profession and organized medicine have not panicked, but remain steadfast in the belief that a physician's first responsibility is to his or her patients and to no one else, and to something called quality of care and, of course, to containing costs as much as possible. But something more will be needed than simply reaffirming principle and reacting piecemeal to crisis piled upon crisis. It will require the marshaling of the special knowledge and skills of the profession and bringing them to bear, not only in the patients' interest but also on the quality and cost of care, on the promotion of health and in the public's interest. The real strength—and power—of the medical profession lies in its special knowledge, skills and expertise and how effectively these are applied in all aspects of health care, including its social, economic and political aspects.

Looked upon in this way, the list of things the medical profession "ought to do" seems virtually limitless. Many specifics have been repeatedly suggested in professional periodicals and in the public communications media. For example, it has been said that only the medical profession has the skill and expertise to identify and eliminate worthless treatments, reduce the iactogenic injuries and disease that sometimes accompany modern diagnosis and treatment, or provide the information needed to correct indefensible variations in the cost of caring for the same conditions with the same results in different locations. It has been suggested that physicians aggressively seek to participate, that the profession bring its knowledge, skills and expertise to bear in the decision-making process at every level of health care, and so begin to counteract the trend to place medical decision making in other hands. Some more specific suggestions that have appeared in this journal include the following: develop computerized patient care data bases so as to measure quality as well as cost of care rendered; explore the concept of "generic" medicine and surgery; promote a problem-solving protocol for the broader problems in health care based on the proved problem-solving techniques a physician uses in a difficult or complex case; develop improved physicians' communication skills with patients and the public; organize patients and their relatives and interested persons in a community into pressure groups to support physicians' efforts in behalf of patients and better patient care.

But the basic problem remains. To do the many things it is said that organized medicine "ought to do," a very large number of things will need to be done at the same time. Perhaps a way to do it is to divide the responsibilities among the many associations in such a fashion that each would be able to contribute a part to the whole of what it is agreed "ought to be done," each in accordance with its own interests, commitment and resources. There are 50 state medical associations and probably hundreds of more-or-less sophisticated county medical societies that could participate, not to mention the specialty societies. If there were some kind of a

master framework to coordinate study and action throughout the profession, then an organizational instrument might be created that could in fact bring the special knowledge and expertise of the medical profession effectively to bear, simultaneously, on so many of the things organized medicine ought to be doing with so many of the presently unstudied and unsolved problems in health care.

MSMW

Screening for Disabilities

ELSEWHERE IN THIS ISSUE Foster and colleagues have provided an excellent description of the activities that physicians should use in their efforts to prevent disabilities or to identify existing disabilities as early as possible. We know why such efforts are important from a medical standpoint. When we cannot actually prevent disabilities, time is of the essence in our efforts to contain and compensate for the effects of a given disability and to hold unnecessary involvement to a minimum.

Where we often fail in medicine, I believe, is in considering the total impact of a disability on the life functioning of our patients. Because our perspective is too physiological, we sometimes miss opportunities to have our medical interventions contribute to improved functioning for the individual person in the world at large. If our choice of medical intervention could be based not only on consideration for the medical condition but also on consideration for keeping a child in school or maintaining a young adult in a vocational program, our patients' well-being would be better served.

Disabilities can affect all aspects of a person's life—educational, employment and social—not just those bracketed off as "health" concerns. Serving patients with disabilities calls for a broad awareness of the nature of disabling conditions in this country and of the service system that is involved with persons with disabilities. For a physician working with disabled patients, this awareness requires the following:

- A knowledge of the facts about disabling conditions. What are the nature and size of the population of persons with disabilities? When are these conditions most likely to occur? How can we be alert to vulnerable periods?
- A knowledge of the resources available for persons with disabilities, locally and in federal and state programs, so that working relationships can be established with the professionals who are or should be involved with a patient at the same time the physician addresses medical needs.

The Population

From 1% to 2% of all newborns have discernible disabilities or developmental defects. This includes visibly obvious structural anomalies such as spina bifida, congenital heart defects that require more subtle examination techniques for detection and problems discovered via biochemical analysis, such as phenylketonuria. Also included are infants having intracranial hemorrhages, respiratory problems requiring ventilation or severe infections occurring during the neonatal period.

Approximately 10% of all children enrolled in this nation's schools are eligible for special education or "related services" under Public Law 94-142, the Education of All Handicapped Children Act of 1975. This includes those with disabling conditions and other developmental problems that interfere with the *education* of a child, including such conditions as relatively mild, transient speech-articulation defects. We seem to be doing well at identifying sensory, cognitive, intellectual or learning problems that directly affect the educational needs of a child, but sometimes children with physiologic disease, motor disorders or emotional problems are less well identified by the education system because the problem does not directly affect the child's educational process.

Approximately 15% of the adults between 18 and 65 years of age in this country are considered disabled to the extent that they do not participate in regular employment. This includes persons affected by severe disabling conditions such as quadriplegia or mental retardation, chronic lower back disabilities, mental illness and those who are malingering.

Approximately 1% of the persons in this country, including some members of the previously described populations, have sensory, cognitive, motor, physiologic or mental health disorders that were manifest before age 22 years and that significantly affect their functional lives. They are known as persons with *developmental disabilities* according to Public Law 98-527, the Developmental Disabilities Act of 1984.

The percentage of persons with developmental disabilities remains fairly constant, both relatively and absolutely. Advances in medical and surgical treatments (such as cardiac surgery) permit a limited number of disabled persons to achieve fully functional lives. Some achieve independence through bioscientific achievements, such as out-of-hospital ventilatory assistance, and others through evolving positive societal attitudes, such as employment opportunities for those with significant retardation. It appears that accidents, degenerative diseases that do not manifest until the teenage years and complications of disease such as arthritis, diabetes and other medical conditions are the principal reasons for additions to the disabled population that cause the rate to remain essentially at 1% of the nation's population over time.

Genetic defects, including chromosomal aberrations, and prenatal environmental causes constitute a large percentage of developmental problems. The majority of prenatal causes remains unknown. At the present time, prenatal identification of such genetic and environmental causes exists for a meaningful but yet small percentage of those who will eventually manifest developmental disabilities. Perinatal causes, especially hypoxia, anoxia and infections, account for a large proportion of all developmental disorders.

An important segment of the developmentally disabled population is made up of children known to have renal disease, cardiomyopathies, muscular disorders, mental illness and other disorders that worsen over time and eventually significantly affect physical and cognitive functions. Knowledgeable physicians and other health professionals initiate screening procedures in their practices to identify their patients who show such signs and symptoms and coordinate or provide the required evaluation and referral services.

Physicians who care for adolescents and young adults often treat the residuals of vehicular accidents, attempted homicides, industrial and construction accidents, diving and other sports-related injuries typical of the fast-paced, action-oriented lives of this segment of our population. This patient cohort's need is not screening for identification, but periodic monitoring to ensure that needed services are available and that the young person is known to all the required educational,

health, vocational and independent-living agencies that can provide appropriate services. Additionally, repetitive depressive episodes, near suicides with mental or physical residuals and eating disorders all have the potential to significantly and permanently affect a young person's life before age 22 years and to qualify that person for services for developmental disability.

Resources

Less than half of the US childhood population regularly visits physicians for child health supervision activities after 36 months of age. This mandates a cooperative process between a child's physician, who has cumulative health and developmental information, and personnel from the child's school who screen and evaluate preschool and school-aged children under PL 94-142 regulations.

In addition, there remains a need for additional physician-initiated clinical activities to effectively screen older children, adolescent and young adult populations to ensure that all persons with developmental disabilities are not only identified but also adequately evaluated and provided with needed services.

But beyond the screening efforts, we need also to make efforts to integrate our medical services with community, state and federal programs that can contribute to the quality of life for patients with disabilities. We should not only be treating the medical problems of a child with spina bifida in our offices, but should also be working closely with school personnel to see that our recommendations for bladder management fit optimally with the child's normal activities and that the school personnel can carry out such recommendations. Does the adolescent we have seen after a suicide attempt have contact with community mental health and family support services, and how can we contribute to the ongoing efforts of those services? How can we steer a high school student with a degenerative neuromuscular disorder toward the vocational services that could help that patient toward a possible career?

This broad approach has not traditionally been within the scope of most clinical practices. In the case of disabling conditions, the awareness of nonmedical needs and resources to meet them is vital to a patient's well-being. For physicians, such integrative efforts offer a way to make the often great challenges of patients with chronic disabilities a shared and more rewarding responsibility.

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Ancient Sources of Lead and Lead Poisoning in the United States Today

LEAD IS ONE of the ancient metals. A lead statue in the British Museum discovered in Turkey dates from 6500 BC.[1] Lead has been mined, smelted and used in cosmetics, internal and topical medicinal preparations, paint pigments and glazes throughout the Old World since earliest recorded history.[2] Elsewhere in this issue, two recent cases of lead poisoning in children are presented—one due to azarcon, a Hispanic folk remedy containing lead tetroxide, and the other due to the close proximity of the child's home to a secondary lead smelter. The physicians handling these cases are to be congratulated. Owing to the nonspecificity of the classic clinical manifestations of plumbism, its diagnosis has baffled physicians from antiquity[2] to recent times. Two recent baffling cases were traced to ancient uses of lead, namely, a lead-glazed ceramic mug[3] and a lead-contaminated health food calcium dietary supplement.[4] The definitive laboratory test for the diagnosis of lead poisoning is a whole blood lead test, which has become widely available only in the past decade. Within the past few months, the National Bureau of Standards has made available a certified standard reference material for blood lead analysis (SRM 955, available from the United States Department of Commerce, National Bureau of Standards, Washington, DC 20234) that should further improve the quality of blood lead data.

Lead-bearing ores often contain silver. Following the discovery about 4000 BC of cupellation, a simple process by which silver can be recovered from lead ores, lead was extensively mined throughout the Old World, mainly for its silver content. Nriagu[2] estimates that more than 40 million tons of lead had been produced by the time of the fall of Rome. Although the fact is not recorded, it is not unlikely that children near ancient lead mines and smelters were poisoned in a manner similar to that reported by Sawyer and colleagues. In this most recent case the physicians, having made the diagnosis, are to be congratulated in particular for having taken the next important step, namely, visiting the child's home to collect environmental samples to identify the child's source(s) of lead. It is this step, together with the reporting of index cases to public health authorities,[5] that is essential to trigger an epidemiologic investigation, which in this case apparently led to closure of the smelter and evacuation of the heavily contaminated adjacent area. Similarly, an alert pediatrician trained in an eastern city where childhood plumbism is endemic recognized clinical plumbism in two children from Kellogg, Idaho, where he had gone to practice. He reported these cases which, in turn, resulted in the discovery of an epidemic of subclinical plumbism due to emissions from a large primary lead smelter in Kellogg.[6]

In addition to children who live near lead smelters, children (and other housemates) of lead workers who bring lead-bearing dust home on their work clothing are also at risk. Several clusters of such cases, particularly in relation to lead and asbestos, have been identified.[7] These cases illustrate the need for physicians to take both environmental and occupational histories. All family members of index cases should be considered regardless of age, and cases should be reported so that appropriate epidemiologic investigations and public health action can be undertaken.

Ceruse (lead carbonate), litharge (lead monoxide) and other oxides of lead and galena (lead sulfide) have been used in the Old World throughout recorded history as cosmetics and basic ingredients in medicaments, nostrums and folk remedies.[2] Lead sulfide is still used today as a black eye cosmetic and is known on the Indian subcontinent as *surma* and in the Arabic world as *kohl*. Recently, severe cases of plumbism in children from both cosmetic[8] and medicinal uses[9] of lead sulfide have been reported. The Greco-Romans used lead carbonate and the oxides of lead primarily in topical medica-

tions and only to a limited extent in internal remedies. The ancient Chinese, however, used lead to a much greater extent in herbal medicines given internally.[2] Furthermore, these concoctions may contain arsenic, mercury or both.

Not surprisingly, some people who come to the United States from Asia, the Middle East and South America bring with them these ancient folk remedies, although they may be reluctant to admit it. For example, the Centers for Disease Control (CDC) have recently reported cases of both lead and arsenic poisoning among Hmong refugees in the United States due to or suspected of being due to imported folk remedies.[10,11] Hmong people residing in the United States are concentrated mainly in San Diego, Fresno and Stockton, California, and Minneapolis.[10] Cases of plumbism due to both Indian[12] and Chinese[13] folk remedies have been identified in the West within the past decade. Preparations containing lead, arsenic or mercury are used in folk medicine, not only as remedies for such complaints as *empacho,* fever and rash, but also as tonics and salves.

While one of the cases reported elsewhere in this issue was due to lead tetroxide (azarcon, also known as *greta*), recent surveillance by the CDC makes it clear that we must extend our horizons beyond Mexico to include immigrants from all parts of Asia. Our horizons must also be extended by the realization that arsenic and mercury may also be present in such folk remedies. It is only 40 years since arsenicals were replaced by penicillin in the treatment of syphilis in the western world. Perhsgen's observation that arsenicals could be found in Belgium in over-the-counter medications as late as 1978 should make the traveler wary.[14] These events present a considerable challenge to physicians and allied health professionals working in concert with leaders of ethnic groups newly arrived in the US, if deeply engrained ancient but dangerous cultural practices are to be changed.

Tetraethyl lead was discovered in the United States by Thomas Midgely in 1921, added to gasoline in 1923 and raised a public health controversy from the very beginning.[15] After the intense public scrutiny of the past 15 years, it appears that this most recent source of widespread low-level environmental contamination by lead will shortly end. The US Environmental Protection Agency has ruled that the lead content of gasoline be reduced to 0.1 grams per gallon by 1 January 1986 and has proposed a complete ban as early as 1988.[16] This is likely to leave lead paint, another ancient use of lead, as the major lead-related public health problem in the United States, particularly in the older housing in the East and the Midwest.[17] Not only are poor children in deteriorated old housing still at risk, but so also are urban homesteaders who renovate old housing.[18] Although it is well known that virtually all housing built in the United States before 1940 contained lead pigment paints, it may not be appreciated that approximately 20% of housing built between 1960 and 1975 contains potentially hazardous amounts of lead on exposed interior surfaces.[19] The distribution of paint containing lead additives (driers and pigments) intended for exposed interior and exterior residential surfaces was finally banned in interstate commerce by the Consumer Products Safety Commission in September 1977.[20] Decades may pass before lead-painted housing is either replaced or totally renovated. Thus, the ancient causes of serious and even fatal lead poisoning—paint, folk remedies and tonics, cosmetics and dangerous lead trades such as lead smelting—remain with us, while one of the most recent discoveries—tetraethyl and tetramethyl lead—departs the scene after a brief stay of about 70 years. Lead is a versatile metal with many uses. This makes it incumbent upon physicians to consider the many possible sources of exposure for a given child[21] and to initiate the environmental investigation necessary to identify the source(s). Reducing or eliminating the source is the cornerstone of therapy for lead poisoning. Primary prevention is, of course, the long-term goal.

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Case Reports

Sonographically Documented Disappearance of Nonimmune Hydrops Fetalis Associated With Maternal Hypertension

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NONIMMUNE HYDROPS FETALIS is a condition of the fetus characterized by varying degrees of anasarca, ascites and pleural and pericardial effusions in a pregnancy without rhesus isoimmunization. Diagnostic ultrasonography has permitted in utero diagnosis of this condition, which is frequently incidental to the original indications for the procedure. We report a case of nonimmune hydrops fetalis associated with maternal pregnancy-induced hypertension that spontaneously resolved over a period of several weeks, coincidental to the resolution of the pregnancy-induced hypertension.

Report of a Case

The patient, a 22-year-old gravida 2, para 1 woman with a previous normal term pregnancy, was having an uncomplicated pregnancy until 28 weeks' gestation when her blood pressure rapidly increased to 134/90 mm of mercury from a level of 110/60 mm of mercury at 12 weeks' gestation. Analysis of her urine showed 1+ protein and she had a 3+ pedal edema. Over the four weeks since her previous office visit, the patient's weight had increased from 56 to 65 kg (123 to 143 lb). Mild polyhydramnios was suspected by a rapid increase in fundal height. Ultrasound examination confirmed the polyhydramnios and showed placental thickening (8 cm), fetal ascites and pleural effusions (Figure 1). The maternal blood type was O Rh positive, with a negative screen for irregular antibodies. VDRL was nonreactive. The rubella titer was 1:80, the toxoplasmosis titer was less than 1:8 and testing for hepatitis B surface antigen was negative. Her hematocrit was 41%. A 24-hour urine collection showed a creatinine clearance of 78 ml per minute and a total protein of 289 mg per 24 hours. The serum albumin level was 2.8 mg per dl.

Over the next two weeks, evidence of maternal pregnancy-induced hypertension cleared with bed rest. In the same time period, ultrasound examinations documented the spontaneous clearing of the nonimmune hydrops fetalis with reabsorption of the effusions, ascites and polyhydramnios (Figure 2). Non-stress testing initiated at the time of the diagnosis of the hydrops fetalis and continued until delivery at 37 weeks consistently showed a reactive fetus without abnormal baseline heart rate or periodic changes. After a spontaneous labor, the patient was delivered of a vigorous 3,300-gram male infant with a cord blood hematocrit of 56% and evidence of a mild hepatitis. The cord blood serum alanine aminotransferase (formerly SGOT) was 74 units per liter (normal to 20) and the lactic dehydrogenase level was 585 units per liter (normal 100 to 225). Total bilirubin level was 9.2 mg per dl (normal 1 to 4) and the IgM was 43 mg per dl (normal 6 to 25). Viral culture of a urine specimen was negative for cytomegalovirus. Cultures of specimens from the throat were negative for adenovirus, enterovirus, echovirus and respiratory syncytial and herpes simplex viruses. The placenta weighed 1,000 grams but was unremarkable on histopathologic examination. The infant remained mildly jaundiced for several weeks with a total bilirubin level of 8.2 mg per dl and a direct fraction of 3.6 mg per dl at three weeks following delivery. At six weeks, the total bilirubin value was 2.2 mg per dl with a direct

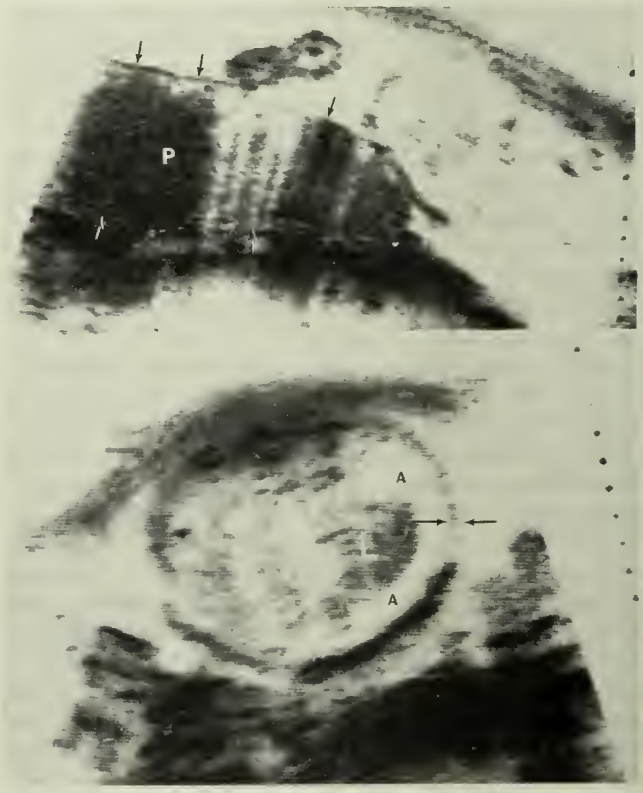

Figure 1.—Top, A longitudinal ultrasound scan shows pronounced placental (P) thickening (8 cm) and polyhydramnios. The margins of the placenta are indicated by arrows. **Bottom,** A transverse scan of the fetal abdomen shows moderate ascites (A). The liver (L) and bowel are outlined by fluid. The thickened abdominal wall is indicated by arrows.

(Robertson L, Ott A, Mack L, et al: Sonographically documented disappearance of nonimmune hydrops fetalis associated with maternal hypertension. West J Med 1985 Sep; 143:382-383)

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fraction of 0.7 mg per dl. At about 2½ years of age, the infant is developing normally.

Discussion

With the continued decline in the incidence of rhesus isoimmunization in the obstetrical population, nonimmunologic causes currently account for most cases of hydrops fetalis. Because of the diverse associations among maternal disease states, fetal congenital anomalies and nonimmune hydrops fetalis, uniform diagnostic criteria and a single unifying pathophysiologic concept have not developed.[1] However, most cases variably present with ultrasound evidence of polyhydramnios, placental thickening, edema of the fetal skin and effusions in the abdominal, pleural and pericardial cavities. Overall, perinatal survival is poor, ranging from 20% to 50%. Maternal pregnancy-induced hypertension when associated with nonimmune hydrops fetalis may be severe, frequently occurs before midpregnancy and is associated with a poor fetal outcome.[2] Although unusual, recurrences of hydrops fetalis in the same patient have been reported. Benign transitory ascites has been reported previously.[3]

The case reported here is unusual in that the hydrops fetalis spontaneously regressed in utero despite sonographic features of more advanced nonimmune hydrops fetalis, which in the past has been associated with a poorer fetal prognosis. It is interesting to speculate that the fetus suffered a congenital viral infection with transient myocarditis, hepatitis and congestive heart failure. This in turn resulted in an increase in placental mass with the appearance of the pregnancy-induced hypertension. As the fetal cardiovascular difficulties cleared, the pregnancy-induced hypertension resolved in the mother. Though the fetus was able to clear the cardiovascular component in utero, complete resolution of the hepatitis required an additional six weeks postpartum.

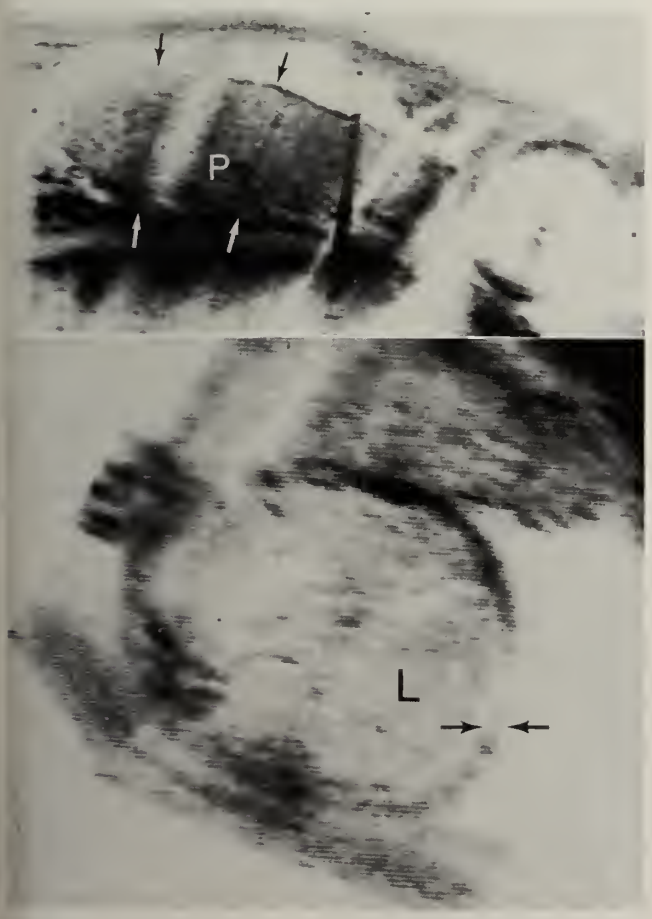

Figure 2.—Top, Scans done two weeks later show a decrease in placental (P) thickness from 8 cm to 6 cm. The margins of placenta are indicated by arrows. **Bottom,** A transverse scan of the fetal abdomen shows resolution of fetal ascites and a decrease in abdominal wall thickness. The abdominal wall is indicated by arrows and the liver by L.

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Hypoventilation in a Case of Nonfamilial Parkinson's Disease

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THE CLINICAL SYNDROME of idiopathic central alveolar hypoventilation is characterized by inadequate automatic ventilation, carbon dioxide retention disproportionate to the degree of mechanical abnormalities of the respiratory system (if any), hypoxemia and cor pulmonale.[1-3] This syndrome has been generally described in association with brain-stem disorders such as bulbar poliomyelitis, medullary infarct and cervical cordotomy.[4,5] Recently, a familial syndrome with parkinsonism and alveolar hypoventilation has been described.[6,7]

We describe the case of a patient with nonfamilial parkinsonism who showed hypoventilation, hypoxemia and cor pulmonale and responded to progesterone administration. This observation may suggest a possible association of hypoventilation with parkinsonism.

Report of a Case

The patient, a 59-year-old woman, was admitted to hospital in November 1979 with respiratory failure. Her major symptom was somnolence, present for at least several weeks before admission; the patient also complained of weakness and mild dyspnea on exertion. She had been diagnosed as having mild Parkinson's disease 15 years previously for

(Darwish RY, Fairshter RD, Vaziri ND, et al: Hypoventilation in a case of nonfamilial Parkinson's disease. West J Med 1985 Sep; 143:383-385)

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ABBREVIATIONS USED IN TEXT

$AaDO_2$ = alveolar-arterial oxygen difference
ECG = electrocardiogram
$Paco_2$ = partial arterial carbon dioxide pressure (tension)
PaO_2 = partial arterial oxygen pressure (tension)

which she was treated with a combination of levodopa, carbidopa and trihexyphenidyl hydrochloride. There was no history of smoking, bronchial asthma or chronic bronchitis. During an outpatient evaluation in 1977, she was noted to have dyspnea and cyanosis. Arterial blood gas analysis done at that time while the patient was breathing room air showed a pH of 7.37, partial arterial oxygen pressure (PaO_2) of 43 mm of mercury, partial arterial carbon dioxide pressure ($Paco_2$) of 60 mm of mercury and calculated bicarbonate 33 mEq per liter. The chest roentgenogram, also taken at that time (two years before the present admission), showed small, bibasilar, patchy opacifications with slight elevation of the diaphragm and mild cardiomegaly. She was treated with a regimen of diuretics and a digitalis preparation.

The family history was negative for Parkinson's disease and other major illnesses. Her current medications consisted of hydrochlorothiazide, 50 mg; digoxin, 0.25 mg daily; carbidopa, 10 mg; levodopa, 100 mg, and trihexyphenidyl HCl (Artane), 2 mg three times a day.

On physical examination she was stuporous with many repetitive periods of apnea and cyanosis during sleep and while awake. The duration of the apneic periods varied somewhat, ranging from 15 to 45 seconds to longer. During prolonged periods of apnea, the patient would become cyanotic and fail to initiate any apparent ventilatory efforts until awakened. The patient was 160 cm (63 in) tall and weighed 59 kg (130 lb); she was not considered obese as her body weight was less than 130% of her predicted body weight.[8] Her blood pressure was 110/70 mm of mercury, pulse rate 96 per minute, rectal temperature 37°C (98.6°F) and respiratory rate 15 per minute. Examination of the head, ears, eyes, nose, throat and neck showed unremarkable findings except for mild arteriovenous crossing on funduscopic examination. Chest excursions were symmetrical, there was no evidence of kyphoscoliosis and the lungs were clear to percussion and auscultation. The heart had a regular rhythm without gallops or murmurs. The abdomen showed no abnormality, extremities were free of edema and trophic changes and peripheral pulses were intact. On neurological examination she was somnolent but had intact cranial nerve function. Bradykinesia was present but there was no cogwheel rigidity. Motor function was intact and muscle tone and strength were normal. Deep tendon reflexes were equal bilaterally and plantar responses were flexor. Sensory modalities were intact and cerebellar functions were physiologic.

Laboratory findings included the following: serum sodium 135, potassium 4.6, chloride 94 and CO_2 content 30 mEq per liter. Blood urea nitrogen was 24, serum creatinine 0.8, glucose 100 and total bilirubin 0.5 mg per dl. Total protein was 6.8, albumin 4 and γ-globulin 2.8 grams per dl; uric acid was 7.1, serum cholesterol 214, calcium 9 and inorganic phosphorus 4 mg per dl; aspartate aminotransferase (formerly SGOT) was 35 U per liter; alanine aminotransferase (formerly SGPT) 30 U per liter and alkaline phosphatase 30 IU per liter. A hemogram showed a hematocrit of 58%, hemoglobin of 18 grams per dl with normochromic normocytic indices and a leukocyte count of 10,300 per μl with neutrophilic polymorphonuclear leukocytes 71%, band forms 1%, lymphocytes 17% and monocytes 11%. Analysis of urine showed no abnormality and a chest x-ray film showed small, bibasilar, patchy opacifications and slight prominence of the pulmonary artery with mild cardiomegaly. An electrocardiogram (ECG) showed a sinus rhythm with a rate of 82 per minute; other ECG findings included increased P-wave amplitude in leads II, III and aV_F, right axis deviation and prominent R waves and inverted T waves in leads V_1 through V_4, suggesting right atrial and right ventricular hypertrophy. Arterial blood gases obtained during an apneic period with the patient breathing room air showed a pH of 7.23, a PaO_2 of 35 mm of mercury, a $Paco_2$ of 77 mm of mercury and calculated bicarbonate of 31 mEq per liter. The alveolar-arterial oxygen gradient ($[Aa]DO_2$) was estimated to be 18 mm of mercury using a standard equation.[9] This normal value of the $(Aa)DO_2$ suggests that the patient's hypoxemia was due to hypoventilation rather than to ventilation-perfusion inequality, as would be expected in patients with primary pulmonary disease.[9]

The erythrocyte sedimentation rate was 26 mm per hour, tests for antinuclear antibodies and anti-DNA antibodies were negative and serum aldolase activity was 5.2 mU per ml (normal, 2.7 to 5.3). An electroencephalogram, a brain scan and cerebrospinal fluid examination showed no abnormalities. Serum thyroxine was 4.6 μg per dl (normal 5 to 12), thyroxine binding globulin was 0.86 mg per dl (normal 0.38 to 1.17) and the free thyroxine index was 3.9 (normal 4 to 14). Pulmonary function studies showed the following: total lung capacity 3.5 liters (85% of predicted), residual volume 1.25 liters (93% of predicted) and vital capacity 2.25 liters (80% of predicted). The ratio of forced expiratory volume in one second to forced vital capacity was normal (70%). Following one minute of voluntary hyperventilation, the $Paco_2$ fell from 53 to 42 mm of mercury, the PaO_2 rose to 87 mm of mercury with a pH of 7.5. Ventilatory response to CO_2, measured by Read's re-breathing method,[10] was 0.2 liters per minute per mm of mercury (normal $\geq$ 0.6).

An endotracheal tube was inserted and the patient was placed on a respirator with considerable improvement of her arterial blood gas measurements and mental state. However, she showed inadequate ventilatory drive and had periods of apnea off the respirator even when awake, although she breathed on command. A repeat thyroid profile showed mild hypothyroidism for which thyroxine, 0.25 mg a day, was administered. Although her thyroid profile was corrected with this treatment (T_4, 6.6 μg per dl; thyroxine binding globulin, 1.25 mg per dl; free thyroxine index, 8.1), no discernible improvement was noted in her ventilatory activity since apneas continued to occur with the same duration and frequency as before the thyroxine treatment and since hypercapnia persisted when the patient was removed from the ventilator.

Following a subsequent trial without an endotracheal tube,

the patient suffered frequent apneic episodes during sleep and while awake and continued to show depressed PaO_2 and elevated $Paco_2$ values. A few weeks later, she had worsened hypoxemia, hypercapnia and respiratory acidemia, although pulmonary parenchymal abnormalities were not discernible on physical examination and chest roentgenographs. A regimen of intramuscular injection of progesterone, 50 mg twice a day, was started in an attempt to enhance her ventilatory drive. Within two weeks, considerable improvement in her clinical state—and presumably also in her ventilatory drive—was noted. Thus, a representative arterial blood gas analysis obtained with the patient breathing room air showed pH 7.36, PaO_2 66 mm of mercury and $Paco_2$ 56 mm of mercury. Oral administration of progesterone, 30 mg a day, was continued with remarkable improvement of her mental state and alveolar hypoventilation. A repeat arterial blood gas analysis done several months later with the patient breathing room air showed pH 7.37, PaO_2 78 mm of mercury, and $Paco_2$ 46 mm of mercury.

Comments

This case is a clear example of hypoventilation syndrome with chronic hypoxemia and hypercapnia, pulmonary hypertension, cor pulmonale and moderate erythremia. Based on the presence of many and prolonged periods of apnea, the patient showed a major feature of the syndrome of central hypoventilation; however, apneic periods may also be seen in cases of obstructive apnea syndrome,[11] which cannot be excluded because polysomnography was not done. Because our patient's medications were not respiratory depressants, the hypoventilation was presumably not related to her medical therapy. The hypoventilation also did not appear to be related to the patient's hypothyroidism since this was mild and not associated with clinically unmistakable myxedema and since improvement in her thyroid function tests was not associated with concurrent clinical improvement in ventilatory state. The patient also complained of weakness and dyspnea, symptoms not typical of diminished respiratory center sensitivity. These symptoms were mild, however, and were not corroborated by the findings of normal muscle strength on physical examination and normal pulmonary function tests.

The clinical features suggesting hypoventilation were confirmed in this patient by diminished respiratory sensitivity to inhaled carbon dioxide. Although chronic hypercapnia per se will reduce ventilatory drive,[9] this patient's retention of CO_2 would appear to be the result rather than the cause of reduced ventilatory drive because her pulmonary function tests were normal and she could greatly reduce her $Paco_2$ by voluntary hyperventilation. Thus, normal pulmonary function tests, a normal alveolar-arterial oxygen difference (calculated on several occasions), a diminished ventilatory response to inhaled CO_2, chronic CO_2 retention without airflow obstruction and the patient's ability to voluntarily hyperventilate and return PaO_2 and $Paco_2$ to normal or near normal levels are all indicative of central hypoventilation. There is no proven mechanism whereby Parkinson's disease could cause central hypoventilation. However, because Parkinson's disease is associated with pathologic abnormalities in the reticular formation of the brain stem, afferent or efferent respiratory center pathways could be involved.[12]

Progesterone is known to centrally stimulate ventilation[13] and its beneficial effects have been shown in patients with the pickwickian syndrome.[14] In this other regard, Sutton and colleagues found that outpatient treatment with progesterone improved both hypoxic and hypercapnic ventilatory drives in seven patients with the pickwickian syndrome, though the effects were only statistically significant on ventilatory response to hypoxia.[14] Based on the above investigations,[12,13] the dramatic and sustained improvement of arterial blood gases with progesterone administration is most compatible with a significant central hypoventilation component in our patient. Nevertheless, although inconstant and probably infrequent,[8,15] there is also evidence that some patients with primarily obstructive apneas may also improve clinically following therapy with medroxyprogesterone. A possible but unproven mechanism for abatement of obstructive apneas might be greater upper airway patency due to increased drive to the upper airway muscles.[8,11]

A familial form of parkinsonism with mental depression and alveolar hypoventilation has been described.[6,7] The earliest and most prominent symptom noted in this condition is mental depression, unresponsive to antidepressant drugs and electroconvulsive therapy. This is often accompanied by exhaustion, sleep disturbances and pronounced weight loss. Symptoms of parkinsonism appear later in the course of the disease and respiratory failure occurs preterminally. In contrast, the clinical features of Parkinson's disease preceded the onset of clinical features of alveolar hypoventilation in our patient, mental depression and weight loss were not observed and no family history of Parkinson's disease could be elicited. Thus, consistent with a few previous reports,[12,16] it appears that substantial hypoventilation, possibly on a central basis, may be associated with Parkinson's disease.

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Ibuprofen-Induced Aseptic Meningitis in a Previously Healthy Patient

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THE INDUCTION of aseptic meningitis by a nonsteroidal anti-inflammatory drug is a well-documented, though rare, occurrence. Until recently,[1] all previously reported cases have occurred in patients with systemic lupus erythematosus,[2-7] mixed connective tissue disease[8] or other autoimmune disorders.[8] The following case represents the first reported occurrence of this syndrome related to ibuprofen use in a previously healthy young man.

Report of a Case

The patient, a 20-year-old man, was in good health until September 1983, when he was diagnosed as having epididymitis. Tetracycline and ibuprofen were prescribed. His epididymitic symptoms resolved shortly afterwards; however, in the ensuing five weeks he had recurring episodes of fever, headache, myalgias and rash. These episodes lasted from one to four days and resolved spontaneously. The patient had taken ibuprofen periodically during that time for tension headaches but the timing and frequency of administration were uncertain.

In October, the patient was admitted for evaluation following such an episode. Cerebrospinal fluid (CSF) analysis then showed a normal opening pressure, glucose and protein; no cells were noted. Blood, cerebrospinal fluid, urine and sputum cultures were negative for bacteria and fungus. His peripheral leukocyte count was 6,200 per μl. In addition, he had negative results on VDRL, antinuclear antibody, rheumatoid factor, heterophile antigen and febrile agglutinins. He remained asymptomatic and was discharged for outpatient follow-up.

Shortly afterward the patient was admitted to hospital. Within an hour of ingesting a single 400-mg ibuprofen tablet, he had the abrupt onset of fever, headache, photophobia and a diffuse nonpruritic erythematous rash. On physical examination on presentation he had a temperature of 40°C (104°F), conjunctival injection, meningismus, a positive Brudzinski's sign and an erythematous maculopapular rash distributed to the torso and neck. Laboratory studies elicited the following values: electrolytes, creatinine and analysis of urine normal; peripheral leukocyte count, 26,000 per μl; erythrocyte sedimentation rate, 10. CSF analysis showed a cloudy fluid with a glucose of 63 mg per dl, protein of 120 mg per dl and leukocyte count of 1,069 per μl, of which 98% were polymorphonuclear forms. No organisms were noted on Gram's stain, india ink or acid-fast stains.

The patient was treated empirically with antibiotics. All symptoms resolved and the peripheral leukocyte count was 7,000 per μl within 12 hours. All cultures of CSF, blood, urine and throat specimens were subsequently negative. The patient declined repeat lumbar puncture. Once again, the following tests were either within normal range or negative: antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate and VDRL.

The patient was discharged with the presumptive diagnosis of aseptic meningitis due to ibuprofen use and advised to avoid nonsteroidal anti-inflammatory drugs. He has had no recurrence of symptoms.

Discussion

This case is notable in several aspects. All previously reported cases but one have occurred in women and have always been associated with some underlying medical illness, especially collagen vascular disease. Our patient was a previously healthy young man who had several episodes of hypersensitivity-like illness that seemed to worsen with each subsequent administration of ibuprofen. Follow-up evaluations have consistently failed to show any systemic illness.

Aseptic meningitis has been reported with ibuprofen, sulindac and tolmetin.[1-9] The close association in the vast majority of these cases with systemic lupus erythematosus or mixed connective tissue disease has led to the suggestion in some reports of an increased susceptibility to drug reactions in these patients. Perera, however, described the only other patient with this clinical syndrome who did not have associated collagen vascular disease or autoimmune illness.[1]

The clinical scenario is quite similar in most of the reported cases. The patients usually have facial flushing, striking conjunctivitis, meningismus and fevers as high as 40°C; some have abdominal pain.[5,7-9] Laboratory studies frequently fail to show a significant leukocytosis or eosinophilia.[8] The cerebrospinal fluid specimen can show a pleocytosis ranging from several hundred to several thousand cells.[9] Unlike the aseptic meningitis seen due to systemic lupus erythematosus or mixed connective tissue disease alone,[4,7,10-12] these patients show a polymorphonuclear predominance in their cerebrospinal fluid. The protein levels are frequently elevated and the cerebrospinal fluid glucose values low. Therefore, the clinical picture is indistinguishable from that of bacterial meningitis.

The cause of this clinical syndrome is unknown. Prostaglandin synthesis inhibition probably does not play a role in the pathogenesis of this illness. The use of other prostaglandin inhibitors in these patients has generally not been associated with the illness, as indicated in previous reports. The data suggest immune-mediated hypersensitivity as the mechanism of injury. This may be related more to the specific characteristics of the involved compound than to its general properties.

Although aseptic meningitis due to the use of a nonsteroidal anti-inflammatory agent is a diagnosis of exclusion, we feel that a careful drug history is important in the evaluation of meningismus. This is especially so in patients with an associated collagen vascular disease. Our present report documents the second case of ibuprofen-induced meningitis in a

(Lawson JM, Grady MJ: Ibuprofen-induced aseptic meningitis in a previously healthy patient. West J Med 1985 Sep; 143:386-387)

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Submitted June 12, 1984.

Reprint requests to LCDR John M. Lawson, MC, USN, c/o Clinical Investigation Dept, Naval Hospital, San Diego, CA 92134.

healthy patient. This entity may be more commonly seen now that ibuprofen is approved for over-the-counter use. In addition, the report also documents the second case of this clinical syndrome in a male patient. The syndrome of aseptic meningitis due to nonsteroidal anti-inflammatory agents is indeed a clinical entity that should be considered in the appropriate clinical setting.

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Human Insulin in the Treatment of Insulin Allergy

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TREATMENT OF DIABETIC PATIENTS with conventional insulins (rather impure preparations containing beef and pork insulin) has led to local allergic manifestations in 5% to 50% of patients and to systemic reactions in 0.2% to 1%.[1,2] The highly purified single-species pork preparations have reduced the incidence of allergic reactions and have been successful in treating up to 70% of patients with established insulin allergy.[1] A likely explanation for this phenomenon is that anti-insulin IgE (the antibodies responsible for immediate-type local allergy and systemic allergy[2]) have a lower avidity for porcine as compared with bovine insulin.[3,4] The same in vitro studies have failed, however, to detect any difference between porcine and human insulin either with respect to binding to preformed IgE[3,4] or in inducing lymphocyte transformation.[4] In addition, human insulin has been reported to be ineffective in five cases of persistent local allergy to porcine insulin[2,5] and to induce de novo production of IgE antibodies, albeit transient and not accompanied by allergic manifestations.[6] It has thus been argued that human insulin would not afford significant improvement over porcine insulin in the treatment of insulin allergy.[4]

(Lorenzi M, Karam JH: Human insulin in the treatment of insulin allergy. West J Med 1985 Sep; 143:387-388)

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Submitted November 14, 1984.

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Report of Three Cases

We wish to report on three patients whose insulin allergy responded promptly and long-lastingly to institution of therapy with biosynthetic human insulin. The clinical characteristics and history of these patients are summarized in Table 1. It can be seen that in one of the patients local allergic symptoms developed despite the fact that purified pork insulin was the first exogenous insulin he can recall having received. The other two patients had probably been sensitized by the past exposure to the beef insulin and proinsulin molecules contained in the conventional preparations, and in these patients allergic manifestations developed at resumption of treatment despite the fact that the insulin administered was now a purified pork preparation.

Human insulin was started at small incremental doses (1 U every four hours) in patient 2, who had the most severe generalized symptoms; in the other two patients it was simply substituted for the previous treatment. Within 24 hours all patients had complete clearing of symptoms and no recurrence during almost a year of observation. The success of human insulin was particularly welcome in the pregnant patient in whom the protracted use of antihistamines was a source of concern.

It is certainly possible that the two patients with systemic allergy would have responded to desensitization and that the local allergic reactions would have spontaneously subsided or eventually responded to desensitization. However, the rate of success of the desensitization procedure is 95% for systemic allergy and only 50% for local allergy,[2] thus leaving a number of patients in a potentially troublesome situation.

TABLE 1.—*Clinical Characteristics of Insulin-Allergic Patients Who Responded to Human Insulin*

Patient	*Sex & Ethnicity*	*Age*	*History of Diabetes*	*Known Allergies*	*Previous Insulin History*	*Insulin History at Onset of Allergy*	*Allergic Manifestations*
1	♀, Filipino	35	GDM×2	None	B-P for GDM in first pregnancy	2 weeks B-P 3 weeks PP	Local induration and urticaria
2	♀, White	60	20 yr	Penicillin	B-P during 2 hospital admissions	1 month PP	Generalized itching and urticaria
3	♂, Mexican	60	18 yr	None	None	2 months PP	Local induration

GDM = gestational diabetes mellitus, B-P = beef-pork insulin, PP = purified pork insulin

Although we do not have a documented explanation for the therapeutic success of human insulin in our patients, we like to speculate with Skyler and co-workers[7] that while the in vitro binding studies have to date only measured association properties of insulin to antibodies, the dissociation rates of various insulins from antibodies could be an important determinant of clinical manifestations of allergy or immune resistance. Thus, human insulin deserves to be further investigated in vitro and at least empirically tested in patients who maintain untoward immunologic reactions while receiving purified pork insulin.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Laser Irradiation for Pain of Charcot-Marie-Tooth Disease

QUESTION:

It is acceptable medical practice to use low-power, helium neon laser irradiation for the treatment of pain associated with Charcot-Marie-Tooth Disease?

OPINION:

In the opinion of the Scientific Advisory Panels on Neurology, Orthopedics and Physical Medicine and Rehabilitation, low-power, helium neon laser irradiation to treat pain associated with Charcot-Marie-Tooth Disease is not considered accepted medical practice. Pain is not a common or prominent symptom in patients with Charcot-Marie-Tooth Disease. In those rare cases in which pain is a problem, there have been no well-designed studies that have proved the need for or efficacy of laser irradiation in its management.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Treatment of Foot Infections in Diabetic Patients

TO THE EDITOR: I read with great interest the brief review of diabetic foot infections by Gleckman and Roth.[1] Treatment of this problem is an important part of my practice and I believe the article contains several significant errors that deserve comment.

The authors have considered the particular aspects of diabetic foot care by primary care physicians and have noted the possible need to consult orthopedists for surgical therapy. In actuality, general and vascular surgeons have traditionally cared for most of these infections. Approximately one fifth of patients with serious infections or nonhealing diabetic ulcers have significant atherosclerosis, with insufficient perfusion of the foot for healing and with the necessity of distal arterial bypass operations for limb salvage. It is notable that the authors have overlooked the need for assessment of the distal circulation by a vascular surgeon in their recommendations for treatment.

The treatment plans recommended for ulcers are misleading. Debridement should be undertaken by a surgeon well versed in the character of these infections, as they frequently track to a deep sequestrum. I have performed too many proximal (major) amputations in limbs inappropriately "whittled" down to bone, due to misconceptions about these infections. Ulcers are invariably neuropathic pressure sores and they deserve similar regimens as would be applied elsewhere in the body, with removal of the inciting trauma as the mainstay of treatment. Casting a neuropathic limb has been reported of value, but there are no good prospective evaluations of this treatment, and I have seen infections worsen with this technique.

The schema of infections noted by Gleckman and Roth is inaccurate. The infections are almost invariably synergistic, an average of three organisms cultured from tissue specimens. Gas-forming infection is rare; it has been present in only two of my last 60 patients. I must allow the term "synergistic necrotizing cellulitis" as Gleckman and Roth have used it for the most common serious infection pattern, but they have placed it last and deemphasized it. Most often, a phlegmon develops, with tracking of necrosis and vascular thrombosis along fascial planes oriented in a dependent manner with gravity. This infection may be incited by an ulcer, but it more commonly occurs with a sequestrum of chronic osteomyelitis or joint infection. It is notable that with antibiotics, diabetic patients can heal bony infection, but that chronic infection and destruction of an interphalangeal or metatarsal-phalangeal joint result in a poorly perfused site which generally cannot be healed except with surgical excision and drainage. True necrotizing fasciitis is very rare.

I must also note my disagreement with the recommendation for routine use of oral clindamycin in the treatment of cellulitis in diabetic feet. Reflecting concern over the induction of pseudomembranous colitis, and with recognition that these antibiotics must be continued for very long periods of time, cephalosporins and tetracyclines have received the widest use in the primary treatment of simple diabetic cellulitis. For infections requiring admission of the patient to hospital, cefoxitin covers most of the organisms present, but serious infections must be initially treated with triple antibiotics or an equivalent regimen until tissue culture specimens define the organisms present. Antibiotics are administered as long as the foot is healing, not for a defined period of six weeks as noted by the authors. As long as the skin is open, there is a portal of entry for recurrent infection, which I have observed to lead to amputation as a complication of premature cessation of therapy.

Prevention, as noted by the authors, is the key to treating diabetic foot infections. Their regimen is acceptable, but soaks should not be encouraged, as scalding may occur easily in neuropathic extremities.

Those who treat diabetic foot problems realize that these problems are difficult, often requiring changes in attitude and life-style by the patient. For surgeons, treatment of these lesions is more art than science. I believe the authors have excessively simplified the problem. Perhaps the most important point to note is that any diabetic patient admitted to hospital for treatment of a foot infection should be seen in consultation by a surgeon interested and versed in the problem, as this will prevent delayed recognition of the complications of these lesions.

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Comparing US and Other Homicide Rates

TO THE EDITOR: In reply to my letter in the February issue,[1] which dealt explicitly and specifically with deaths from handguns, Dr David C. Stolinsky[2] extends the argument to all homicides and suicides regardless of the weapon employed.

Confusing a subset with the whole is logically fallacious and obscures a major group of potentially preventable deaths, namely those inflicted with handguns.

My letter made two assertions, both of which are readily substantiated. First, each year more than 20,000 Americans die from handgun violence. Collated data[3] from the FBI Uniform Crime Reports, The National Safety Council and the National Center for Health Statistics show that this figure was relatively stable from 1969 to 1979, and there was no major change for homicide alone through 1982.[4] Second, the per capita death rate from handguns is about 100 times higher in the United States than in comparable western countries. Less precision is possible here because most European countries, faced with a lesser problem, do not separate handguns as a category of weapon in their published statistics of violent deaths. Until 1973 firearms deaths were reported for England and Wales.[5] In that year there were 37 firearms homicides and 172 suicides; in the United States the figures were 13,072[6] and 13,317.[3] This yields a per capita rate around 30 times higher in the United States which is an underestimate of the relative rate for handgun-inflicted deaths because the proportion of handguns to total firearms used in these incidents is higher in the United States than in the United Kingdom. In 1979 there were 10,728 verifiable handgun homicides in the United States, 52 in Canada, 8 in Great Britain, 48 in Japan, 21 in Sweden, 34 in Switzerland and 42 in West Germany.[7] These translate to per capita handgun-inflicted homicide rates 9 to 330 times higher in the United States.

No one in his or her right mind would claim that the United States has the highest homicide rate in the world, so Dr Stolinsky is safe in attacking that straw man, but an egregious error occurs in his analysis of homicides. Stolinsky illustrates his contention that the United States does not have a homicide rate higher than other western nations by comparing Sweden with the United States. He uses homicide rates for the United States from the *FBI Law Enforcement Bulletin* but draws figures for Sweden from the rubric BE50 in the *Demographic Yearbook*. BE50 includes conditions other than homicide; AM54 is homicide. A complete list of available rates for western European countries, the United States, Canada, Australia and New Zealand is given in Table 1. The reader may find this gives a more meaningful comparison with countries similar to the United States than Dr Stolinsky's selective extracts. Comparing the United States with the emerging African nation of Zimbabwe during a period of armed insurrection is unlikely to help identify preventable causes of death in the United States.

TABLE 1.—*Homicide Rates for Various Western Countries* (per 100,000 Population)

Country	*Violent Death Other Than Accident or Suicide (BE50)*	*Homicide (AM54)*
United States	11.0	9.1*
Sweden	8.8	
Finland	6.7	
Canada	6.2	
Denmark	5.4	
Ireland	3.6	
Belgium	2.4	
Switzerland	2.4	
Norway	2.3	
Portugal	2.1	
Italy	1.6	
Spain	1.1	
Australia		1.9
New Zealand		1.3
Austria		1.3
West Germany		1.3
France		1.0
Greece		0.8
Netherlands		0.8
England and Wales		0.4

*From reference 4 All other figures are from reference 8

Every word in Dr Stolinsky's final paragraph is to be commended, although I trust that logical blunders such as confusion of "some" and "all," selective quotation of data and failure to compare like with like are not endemic among physicians in Los Angeles.

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Reexamining the Roles of Physicians

To the Editor: I read the article about the pesticide poisoning of a group of Salinas, California, field workers in the April issue[1] with sadness. Included in this well-written clinical article, it seems to me, is a request for all of us to reexamine our roles as physicians. How are we to respond to such an article?

The authors describe the clinical illnesses and treatment of 23 field workers who were tying up cauliflower leaves only six hours after the field had been sprayed with organophosphates. One worker was a 9-year-old child, another a 72-year-old man and a third a pregnant woman. All were ill with blurred vision, eye irritation, dizziness, weakness, disorientation, headache, nausea and vomiting. Several had muscle cramps and four were admitted to hospital, including one comatose worker. Most of the symptoms were gone in a month, but the blurred vision, headaches, weakness and anorexia lasted throughout the 4½ months of follow-up.

I wonder how such symptoms affected the schoolwork of the 9-year-old? What fears were the authors expressing when the pregnant worker's baby was described as an "apparently healthy infant"? I wonder how desperate the economic needs of these people were to have led six of them to another cauliflower field two years later and to find themselves again the subjects of a medical report about organophosphate residue poisoning?

Is such a report only a medical curiosity to most physicians who live and work in urban areas? Or do we as physi-

cians have any role in looking for, and possibly addressing, root causes of such a tragedy? When we advise our patients about diet, does such an article have any relevance beyond the nutrient value of cauliflower and the need to wash off pesticides? Should medical associations consider taking a position—as we have already done with boxing—about control of pesticide use, about child labor or about social and economic conditions that may force children, older people or pregnant women to take such grave health risks?

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Vascular Source of Impotence

To the Editor: In the article "Evaluation of impotence in Older Men" by Davis and colleagues in the April issue,[1] two old and simple tests for a vascular source of impotence were ignored. Ever since Leriche's classic paper on occlusion of the aortic bifurcation 45 years ago,[2] many clinicians check the pulses in the groin by simple palpation and listen through an ordinary stethoscope for a bruit in the iliac and femoral arteries. In the majority of cases these clinical tests will reveal a source, in the iliac arterial system, of arterial insufficiency producing impotence. In many of these patients normal sexual function may be restored by an arterial bypass procedure.

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Dangers of Ocular Instillation of Medications

To the Editor: I applaud Dr Strauss' efforts to direct your readers' attention to the potential for drug absorption from mucosal surfaces.[1] Furthermore, I agree that the application of drugs to the mucosal membranes of patients during emergent situations before intravenous access can be established is an interesting application derived, in part, from his case report. I must take exception, however, with the last sentence of his article, "Certainly the nasal mucosa and the underside of the lip and tongue are well-established routes for drugs; might not the eye provide yet another alternative?" To this concluding query, I reply emphatically—No!

There is no question that significant systemic levels of drug may be achieved with even the most dilute of our commercially prepared, cardiovascular-active, ophthalmic medications during routine ophthalmic therapy.[2] Furthermore, these drug levels have on occasion been associated with clinically very significant systemic pharmacologic effects including death.[3] To use these clinical observations to propose that "the eye" might provide yet another route for drug administration, however, ignores the mechanism of systemic drug absorption following eye drop administration and the tremendous potential toxicity for the eye.

Following ocular instillation of medications, there is a natural flow of the drug-laden tears from the conjunctival cul de sac to the nasal mucosa via the nasolacrimal outflow system. The vascular nasal mucosa provides an excellent absorptive surface. Therefore, it is this outflow mechanism that accounts for the systemic absorption of drugs following topical instillation. It is important to recognize this system during eye drop therapy because the simple closure of the eye for 60 seconds following eye drop instillation and application of gentle pressure over the canaliculi which provide entrance to this outflow system can reduce systemic absorption of eye drops.[4] Therefore, if drug absorption from the nasal mucosa is desired, the direct application of drugs to the nasal mucosa by routine nasal insufflation might be reasonable. To coincidentally expose "the eye" to this therapy, however, provides an unnecessary potential for ocular toxicity.

Many drugs used to manipulate the autonomic nervous system have multiple pharmacologic effects on the eye.[5] In fact, even dopamine can be used, in eye drop form, to achieve ocular pharmacologic effects.[6] Furthermore, it appears dopamine, given systemically, can have toxic effects on the eye.[7] Therefore, it could be detrimental for the health of the eye and the patient's vision to instill cardiac drugs during emergent situations. The danger is even greater during cardiopulmonary resuscitation when the patients' natural reflexes to protect their eyes are absent.

Finally, I find it surprising there is no mention of an ocular examination in this case report. Was there a change in vision? How high (low?) was the intraocular pressure? Was there evidence of anisocoria? Did the retinal vessels show evidence of vasoconstriction?

In conclusion, I implore the author and your readers not to take the quotation "Drink to me only with thine eyes"[8] literally.

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Usefulness of Direct Linkage of Physicians' Office Terminals to a Hospital Laboratory Computer

To the Editor: Within recent years, clinical laboratories have used computers to handle laboratory data and facilitate reporting. An extension of the process has been the application of technology to allow remote access of the data from sites away from the hospital, such as physicians' offices. For

the past two years, the clinical laboratory at Mount Zion Hospital and Medical Center, San Francisco, has been linked to several physicians' offices by means of remote terminals.

The clinical laboratory uses a Data General C330 Eclipse central processing unit and Medical Information Technology software for workload organization and data management. The laboratory services include hematology, chemistry, virology, microbiology and blood banking. The data are available at several on-site peripheral terminals.

The terminals used consist of a single unit housing a keyboard, 80 column printer, 300 baud modem and power supply. Five such units are in use. The modem is directly connected to the telephone line.

The operation is simple to initiate. The hospital computer phone is dialed. When the characteristic tone is heard, indicating that contact has been established, the power and modem are switched on. The printer requests entry codes which are then typed in. If the entry codes are appropriate, it is possible to obtain information by selecting a given test or a given patient. A permanent copy is obtained and, by pressing the copy switch on the terminal, the data stored in the buffer are presented to the printer again for a second copy.

The clinical usefulness of personal computers in the physician's home linked by telephone to the laboratory computer has recently been described.[1] This report relates to linking terminals in physicians' offices with the laboratory computer.

Both physicians and their patients benefit by the availability of inpatient and outpatient lab data 24 hours per day. The information is available as soon as the tests are completed and entered into the computer. Thus, there is no need to initiate a communication with various clerical personnel in the laboratory to obtain reports and, accordingly, errors and time spent awaiting responses are decreased.

A physician can access the entire laboratory record, thereby eliminating the necessity for several calls to different laboratory departments such as hematology or virology.

There are several clinical applications of remote accessing of the laboratory computer. Prior laboratory data on a new office patient are readily available by means of the remote linkage to the laboratory computer. This facilitates the doctor's evaluation of the patient.

Another advantage of the remote accessing of the laboratory computer is the ability to quickly obtain test results such as prothrombin time, potassium, digoxin and quinidine levels. Patients frequently request reports that have not yet arrived in the doctor's office by the usual route of delivery. This information is easily accessible from the laboratory computer.

Patients in hospital can also be followed with the office terminal. Data can be assembled by the computer and printed by a local terminal. It is frequently useful to see the chronological arrangement of hemoglobins, hematocrits, enzymes, liver function tests and so forth.

Summary

Remote accessing of inpatient and outpatient laboratory data 24 hours a day allows the physician to obtain important information rapidly. Errors and inconveniences caused by intermediary personnel are reduced. Thus, the physician and the patient are brought in closer contact with the data by means of remote telephone linkage of the doctor's office to the hospital computer.

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Satan's Malady

(A Cry for Help From a Fellow Physician Who Shall Be Nameless)

My bladder is my master; I shall know no rest.

It tormenteth my days with frequency: it maketh my nights hellish.

From raging cystic waters, misery and embarrassment follow me, no matter wherst I go.

Yea, though I subsist on but sips of fluids with but scant morsels of food and avoideth alcohol and condiments, constant torment is my measure; interstitial cystitis is with me; it brings everlasting distress and duress.

I goeth to the lairs of urologists: they peek, peer, shake their heads and say with no enthusiasm, "Come back in a year"; then I seek the supertherapists: all say, "No help here."

Sadly, struggling with odors, damp and zippers shall follow me all the days of my life: and I shall dwell handy to a commode for ever.

ANON

Topics in Primary Care Medicine

An Approach to Peripheral Lymphadenopathy in Adult Patients

GRETCHEN KUNITZ, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

Practicing internists or general practitioners are frequently faced with the task of evaluating an adult patient with peripheral lymphadenopathy. Peripheral adenopathy, by definition, is detectable by palpation. Lymph nodes in the mediastinum or retroperitoneum are central rather than peripheral and will not be discussed in this review. Whether regional or generalized, adenopathy may be the presenting complaint of patients with a wide variety of underlying illnesses. Although many of these illnesses are self-limited or easily treated, the incidence of lymphatic malignancy increases steadily with age. Retrospective reviews of peripheral lymph node biopsies in patients younger than 25 years of age repeatedly have shown a less than 20% incidence of malignancy. In contrast, in the over-50 age group, 55% to 80% of biopsies have shown a malignant process due to either primary lymphoma or metastatic carcinoma.

When a patient initially complains of localized or generalized swelling or when a practitioner first discovers presumptive adenopathy, the following questions must be asked: Is the swelling adenopathy? If adenopathy is present, what is the likelihood that malignancy is present? What diagnostic tests are indicated? Is biopsy necessary and, if so, when should it be done? The answers to these questions will vary considerably among patients. A thorough review of patient characteristics such as age and duration and severity of symptoms combined with an assessment of the character and location of the adenopathy will aid practitioners in their evaluation and diagnostic plan. The intent of this review is to provide a framework for diagnostic evaluation.

Is the Swelling Adenopathy?

On initial evaluation it is often difficult to distinguish actual adenopathy from swelling due to other causes. Neck cellulitis, periodontal abscess, thyroglossal duct cyst or parotitis may mimic cervical adenopathy. Similarly, an inguinal hernia or enlarged axillary sweat gland may be mistakenly identified as an enlarged node.

Determining the Likelihood of Malignancy

As a working definition, it is useful to consider the presence of one or more nodes greater than 1 cm in size or multiple smaller nodes as grounds for further investigation. In addition to evaluating lymph node *size*, the *character* of the adenopathy must be evaluated. Although tender nodes are often indicative of an infectious process and rock-hard or rubbery nodes suggestive of malignancy, these axioms should serve as guidelines rather than as absolute rules. The *location* of the node is of diagnostic importance, as malignant tumors are most commonly found in cervical and supraclavicular sites. Isolated inguinal adenopathy is rarely associated with malignancy. Also important are the *duration* and *rate of growth* of the adenopathy. Steadily enlarging nodes over a period of months are more suspicious than newly discovered nodes that change little in size in the initial weeks of evaluation. Once the characteristics of the nodes have been evaluated, the characteristics of the patient need careful consideration. Bacterial infection accounts for 75% to 85% of adenopathy in the pediatric age group. Thus, a 10-year-old who presents with a tender, enlarged cervical node initially requires aspiration for culture rather than excisional biopsy. In a recent retrospective study of 123 patients in the 9- to 25-year age group undergoing lymph node biopsy, lymph node size greater than 2 cm or an abnormal chest radiograph correlated with the finding of granuloma or tumor at biopsy (or, in some cases, both). A history of ear, nose or throat symptoms correlated with the absence of these biopsy findings. Discriminate analysis

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ABBREVIATIONS USED IN TEXT
AIDS = acquired immunodeficiency syndrome
EBV = Epstein-Barr virus

showed a wide range of other symptoms and signs to be unhelpful in predicting which biopsy specimens would show a granulomatous or malignant process. In an older adolescent or adult patient, an assessment based on patient and nodal characteristics is required. Reviewing the major causes of adenopathy by region will aid in formulating a diagnostic plan.

Cervical Adenopathy

Of the hundreds of lymph nodes composing the lymphatic system, the cervical nodes are most often noted by both the patient and practitioner to be enlarged. The most common cause of cervical adenopathy is bacterial or viral infection of the face or oropharynx. A careful examination of the throat and mouth may show the primary source of infection, thus mitigating the need for further evaluation.

With the recent influx of immigrants from South America and Southeast Asia, the incidence of tuberculosis in the United States has increased. Cervical adenopathy may be the presenting complaint of patients infected with *Mycobacterium tuberculosis*.

The common house cat is the definitive host of the protozoan intracellular parasite causing toxoplasmosis. Following contact with cat feces, a cervical or generalized adenopathy may develop. Although usually asymptomatic, this adenopathy occasionally is associated with low-grade fever, malaise and hepatosplenomegaly. The diagnosis rests on detecting serum IgM antibodies. A titer of greater than 1:80 or a fourfold or greater rise in paired serum specimens establishes the diagnosis.

Infectious mononucleosis caused by the Epstein-Barr virus (EBV) is an acute self-limited illness of young adults. It is characterized by fever, pharyngitis, splenomegaly and posterior cervical adenopathy. The adenopathy may persist for many weeks and typically the nodes are firm and tender to palpation. A physician who conducts a superficial examination of a patient with mononucleosis erroneously may prescribe antibiotic therapy for a presumptive bacterial pharyngitis. In as many as 80% of patients with mononucleosis a maculopapular skin rash develops when they are treated with ampicillin. The diagnosis of mononucleosis rests on recording a leukocytosis with increased numbers of atypical lymphocytes in conjunction with a positive heterophil antibody or Monospot slide test. Of these two tests, the Monospot is both more sensitive and more specific.

A clinical syndrome similar to mononucleosis is associated with cytomegalovirus. The adenopathy and pharyngitis associated with this illness are less pronounced than those associated with EBV. The diagnosis is confirmed by recording a fourfold rise in complement-fixing titers or by cytologic examination of a tissue or urine specimen for cytomegalic cells with intranuclear inclusions. Patients with this syndrome are heterophil antibody-negative.

Various malignant conditions may present with localized cervical adenopathy. Although this occurs most commonly with Hodgkin's disease, it may also occur with other lymphomas or leukemias or, rarely, with thyroid or nasopharyngeal carcinomas.

Preauricular and Postauricular Adenopathy

The differential diagnosis of isolated preauricular and postauricular adenopathy is limited to several common infections. Bacterial or viral conjunctivitis and infections of the eyelid or sinus tracts may result in painful enlargement of the preauricular nodes. Before the widespread use of rubella vaccine in the United States, postauricular adenopathy was commonly seen. The adenopathy may occur as early as a week before the appearance of the typical rash. The diagnosis is confirmed by recording a fourfold rise in serologic titers. The other major causes of postauricular adenopathy are infections of the scalp or ear and postauricular sinus tracts.

Supraclavicular Adenopathy

Most enlarged supraclavicular nodes are associated with malignancy. The left supraclavicular node (Virchow's or sentinel node) drains the lymphatic system of the abdomen, kidney and pelvis, whereas the right-sided node drains the mediastinum, lungs and esophagus. Because they lie behind the clavicular head of the sternocleidomastoid muscle, these nodes often go undetected on routine physical examinations. Asking a patient to do a Valsalva maneuver may facilitate detection.

Axillary Adenopathy

Axillary adenopathy is most commonly associated with bacterial infections of the upper extremity and cancers of the breast. *Mycobacterium marinum* (fishtank granuloma) and sporotrichosis are uncommon causes of axillary adenopathy. Another cause of axillary adenopathy is cat-scratch disease, a usually benign, self-limited illness thought to be caused by a pleomorphic Gram-negative bacterium. The adenopathy appears within one to two weeks of the initial scratch and may persist for months. Associated fever, malaise, myalgias or encephalitis are rare. As there are no serologic tests to document infection with cat-scratch disease, this remains a diagnosis of exclusion. Brucellosis, sporotrichosis and, in rare instances, non-Hodgkin's lymphoma also may present with isolated axillary adenopathy.

Inguinal Adenopathy

It is useful to separate the causes of inguinal adenopathy into sexually and nonsexually transmitted cases (Table 1).

Sexually transmitted diseases. In urban general medical practice, most cases of inguinal adenopathy are caused by the sexually transmitted diseases of syphilis, herpes simplex, gonorrhea, chancroid, lymphogranuloma venereum and granuloma inguinale.

TABLE 1.—*Causes of Inguinal Adenopathy*

Sexually Transmitted Diseases	*Nonsexually Transmitted Diseases*
Syphilis	Lower extremity infection
Herpes simplex	Cat-scratch disease
Gonorrhea	Bubonic plague
Chancroid	Tularemia
Lymphogranuloma venereum	Lymphoma
Granuloma inguinale	Pelvic malignancy

The primary chancre of syphilis develops three to four weeks after exposure to *Treponema pallidum.* Bilateral inguinal adenopathy develops in 50% to 70% of patients about a week after appearance of the chancre. The nodes typically are nontender and firm and in women may be absent if only the deep inguinal system is affected. This regional adenopathy of primary syphilis must be distinguished from the generalized adenopathy of secondary lues, occurring two to ten weeks postchancre. Diagnosis rests on darkfield examination of the primary lesion or on positive serologic tests.

The initial genital infection with herpes simplex type 2 invariably presents with vesicular eruptions and painful bilateral inguinal adenopathy. The adenopathy may persist for as long as six weeks after the initial infection. Recurrent outbreaks of genital herpes are associated with variable degrees of adenopathy.

Gonococcal urethritis may be associated with painful bilateral inguinal adenopathy, but, more commonly, no adenopathy is present. The painful adenopathy seen in conjunction with chancroid infection is unilateral, occurring simultaneously with, or shortly after, the appearance of a genital ulcer. Suppuration occurs in as many as 50% of infected patients. Diagnosis rests on finding Gram-negative bacteria or by tissue culture of the organism, *Hemophilus ducreyi.*

Lymphogranuloma venereum infection, caused by *Chlamydia trachomatis,* frequently presents with painful inguinal adenopathy two to six weeks after exposure. The genital chancre often goes unnoticed and the patient seeks medical attention because of the adenopathy. In 70% of cases, the adenopathy is unilateral. In men, a large painful bubo grooved by the inguinal ligament (inguinal groove sign) may develop. This rarely occurs in women. Concurrent proctitis, rectal abscess or fistula may be seen, and in 5% of patients chronic adenopathy develops.

The inguinal adenopathy seen in conjunction with granuloma inguinale is typically a chronic indolent enlargement caused by deposition of subcutaneous granulation tissue. Diagnosis rests on histologically documenting Donovan bodies and granulation tissue.

Nonsexually transmitted diseases. Infections of the lower extremity may cause inguinal adenopathy and should be carefully looked for during the physical examination. From 10% to 25% of patients with cat-scratch disease present with inguinal adenopathy, presumably due to a prior cat scratch in the lower extremity. Similarly, a bite to the lower extremity by a flea infected with *Yersinia pestis* results in bubonic plague, which is also associated with a unilateral inflammatory adenopathy. Although an uncommon disease affecting from 2 to 20 Americans yearly, mortality approaches 50% to 90% in the untreated patients. Cultures of nodal aspirate and blood specimens are essential for an early diagnosis. Tularemia is associated with an ulcerated painless papule at the site of inoculation, followed by tender regional adenopathy. The incidence of tularemia has increased steadily since 1975, with 200 to 300 cases reported yearly in the United States. In rare cases, lymphoma may present with isolated inguinal adenopathy.

Generalized Adenopathy

While a comprehensive discussion of generalized lymphadenopathy is beyond the scope of this review, the differential diagnosis is presented in Table 2 and is usefully divided into infectious causes, malignant tumors, collagen vascular diseases, dermopathies and hypersensitivity reactions, which are commonly drug-induced. Among gay men and intravenous drug users, generalized adenopathy may herald the onset of the acquired immunodeficiency syndrome. In rare cases, sarcoidosis, hyperthyroidism or the lipid storage diseases may result in general adenopathy.

TABLE 2.—*Differential Diagnoses for Generalized Lymphadenopathy*

Infections	Bacteremia, miliary tuberculosis, brucellosis, leptospirosis, syphilis, tularemia, histoplasmosis, sporotrichosis, mononucleosis, typhoid, leprosy, viral syndromes
Malignancy	Myeloproliferative, lymphoproliferative
Inflammatory	Lupus erythematosus, rheumatoid arthritis
Metabolic	Hyperthyroidism, lipidoses
Dermopathic	Eczema, skin rash
Other	Angioimmunoblastic reactions, phenytoin (Dilantin) hypersensitivity, acquired immunodeficiency syndrome or related condition, sarcoidosis

When working up a patient with diffuse adenopathy, the practitioner should take a medical history that includes sexual preference, occupational and travel history, use of drugs and a complete review of systems. In conjunction with a meticulous physical examination, the lengthy list of causes of generalized adenopathy can usually be narrowed considerably.

Use of Diagnostic Tests

A logical approach to a diagnostic evaluation must take into account salient features of each patient's history combined with the clinical features of adenopathy. As it is neither cost-efficient nor acceptable to patients to do an exhaustive evaluation at the first discovery of adenopathy, the practitioner must determine the extent and rapidity of diagnostic testing to use in each individual case.

In 1978 Greenfield and Jordan developed an algorithm for the investigation of lymphadenopathy. They recommended an initial search for infectious processes, reserving biopsy for those patients with prominent systemic symptoms or adenopathy persisting for more than a week (in the absence of documented infection or drug reaction). This algorithm serves as a useful starting point in evaluating the case of an adult or adolescent patient with lymphadenopathy.

The initial laboratory evaluation in all patients should include a complete blood count. Elevations of the sedimentation rate or hepatic aminotransferase or alkaline phosphatase levels may be present in a patient with lymphoma or metastatic carcinoma, but these tests are nonspecific. A chest radiograph is often useful in that 20% of patients with lymphomas will show abnormalities, as will patients with sarcoidosis, fungal disease or other malignant processes. Mammography is recommended in a woman who presents with axillary adenopathy.

A homosexual man or intravenous drug user with lymphadenopathy presents special problems. In 1981 when large numbers of cases of the acquired immunodeficiency syndrome (AIDS) were first recognized, lymphadenopathy was reported in nearly 50% of patients with Kaposi's sarcoma and 25% of patients with *Pneumocystis* pneumonia. It has subsequently been noted that male homosexuals (and intravenous

drug users and hemophiliacs) frequently have persistent generalized adenopathy. Although the adenopathy may be associated with both neoplastic and infectious conditions, the vast majority of these patients who have lymph node biopsy show a nonspecific pattern of lymphoid hyperplasia.

The exact incidence of generalized adenopathy in the male homosexual population is unknown and it is unclear what percentage of patients with adenopathy will progress to opportunistic infection or neoplasm. Of 200 male homosexual patients with adenopathy evaluated prospectively by Abrams and co-workers in San Francisco and followed for a mean of 28 months, AIDS has developed in 16 (8%) (D. I. Abrams, MD, oral communication, June 1985). Rates of progression noted by other observers have ranged from 1% to 19%. As of May 1985, of 1,100 patients followed nationally for a mean of 20 months, AIDS has developed in 111 (D. I. Abrams, MD, oral communication, June 1985). In the San Francisco cohort, oral candidiasis, infections with herpes zoster, peripheral cytopenia and elevation of the erythrocyte sedimentation rate were found with greater frequency in the cases eventually progressing to AIDS. Other routine laboratory values or clinical variables were not predictive of outcome.

Given these data, it seems reasonable to search for occult malignancy or infection in a homosexual man or intravenous drug abuser who has diffuse lymphadenopathy, hematologic abnormalities, elevated sedimentation rates, oral thrush or herpes zoster. A lymph node biopsy should be reserved for this subset of patients as the yield from biopsy of enlarged nodes in most homosexual men is likely to be low.

When to Do a Biopsy

If an infectious workup is nondiagnostic and the patient has a persistent or progressive adenopathy of unknown cause, a biopsy is indicated. Determining exactly when to proceed with a biopsy is often difficult. As cancers are most commonly found in cervical and supraclavicular nodes, it is reasonable to do an earlier biopsy in a patient with adenopathy localized to these sites. Examination of the ears, nose and throat should be done before a biopsy in a patient with prominent cervical nodes. A woman with prominent axillary adenopathy also warrants an early biopsy, as does an older patient with diffuse, firm adenopathy. Generally speaking, the presence of significant localized adenopathy of longer than two to three weeks' duration without a documented infectious cause is grounds for a biopsy in *all* patients, regardless of age. The presence of diffuse adenopathy in the absence of a known drug reaction, infection or rheumatologic disease also warrants a biopsy.

TABLE 3.—*Diagnostic Yield of Lymph Node Biopsy*

Biopsy Results	*Percent*
Diagnostic	50-63
Nondiagnostic	37-53
Children, excellent prognosis	...
Adults, disease will develop	25-50
lymphoma will develop	20
Problems in diagnosis include	
Poor choice of biopsy site	
Poor surgical technique	
Poor processing	
Poor interpretation	

A lymph node biopsy can be an extremely useful procedure. The internist, surgeon and pathologist should work closely from the outset to assure maximum yield. In several recent reviews the diagnostic yield from peripheral lymph node biopsy in adults has been shown to be 37% to 63% (Table 3). In patients whose initial biopsies are nondiagnostic, a repeat biopsy is often useful. From 25% to 50% of these patients will show evidence of disease on repeat biopsy and a substantial portion (20%) of this group will be diagnosed with lymphoma. The choice of the node from which a biopsy will be taken and the proper biopsy technique are crucial. Generally speaking, it is best to choose the largest accessible node. Ideally, the entire node can be dissected for delivery to the pathologist. If pus or caseation is present, smears and cultures for bacteria and fungi are indicated. Frozen sections help in the diagnosis of nonlymphomatous malignancy, whereas specially stained slides are required for the diagnosis of lymphoma.

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Which Hospital Services Are Most Overused? Results From a Medical Audit

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When we assessed the extent of unnecessary ordering of clinical services by medical house staff at a large university hospital, 21% of services were judged to be unwarranted. Most overordered were nuclear medicine services, followed by laboratory tests. Because of their large volume, clinical laboratory services accounted for 78% of all unwarranted orders. Unwarranted use of hospital services is substantial and variable among physicians and services. This study confirms the value of medical record reviews for documenting the need for and guiding the course of hospital cost-containment programs.

(Myers LP, Chapman SA, McPhee SJ, et al: Which hospital services are most overused? Results from a medical audit [Health Care Delivery]. West J Med 1985 Sep; 143:397-398)

Prospective reimbursement by Medicare and other payors gives acute care hospitals a financial incentive to reduce unnecessary costs. We describe the extent of unnecessary service use by medical house staff at a large teaching hospital. Our study provides a fuller documentation of excessive use of hospital services than was available previously[1-3] and we describe an easily applied method to evaluate overuse.

Methods

We report results from medical record reviews conducted on the medical service of the University of California, San Francisco, Hospital between July 1980 and June 1982.[4] The reviews were used as teaching material for a larger house-staff education program and were not designed to measure overall practice patterns.

A total of 11 full-time salaried faculty general internists plus 4 chief residents conducted weekly medical record reviews. Reviewers audited medical records on an average of twice a month, one record each time. Reviewers were trained in the medical record review process and compared for initial inter-reviewer reliability.

After the medical records were selected and abstracted, the reviewers evaluated the abstracted records. Patient records were chosen to ensure that patient care decisions could be attributed to house staff. Thus, records of patients whose care was supervised by private physicians or who were treated in the intensive care unit were excluded.

Quantity and date ordered of all services were recorded on an abstraction form using a method developed by Martin and co-workers.[5] All laboratory tests, radiologic procedures, respiratory and physical therapy services, selected nursing tasks and other services, such as electrocardiograms and catheterizations, were listed. Also noted was whether a laboratory test was ordered *stat*—that is, requesting immediate processing. A test panel was counted as a single test.

Reviewers used patients' medical records and implicit criteria patterned after those of Dixon and Laszlo[6] to judge clinical necessity of each service ordered. Clinical indications for immediate processing were rated separately. Reviewers also were asked to indicate where needed services were omitted.

Data collected included date, reviewer, house officer and reviewer rating for each service ordered. The percentage of services rated unnecessary was calculated for total services ordered, for subsets of services such as laboratory, radiology and nursing and for individual services.

Results

In all, 173 patient cases were reviewed. Gastrointestinal and respiratory diagnoses were most common (25% and 24% of cases, respectively), followed by metabolic (13%), renal (10%) and hematologic (9%) disorders. Reviewers each conducted an average of 11 medical record reviews, spending an average of 24 minutes auditing each record.

Table 1 displays the number and percentage of services

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TABLE 1.—*Percent of Unnecessary Orders for Hospital Services for 173 Medicine Patients, July 1980 Through June 1982*

Service	Total Number of Orders	Percent Rated Unnecessary
TOTAL SERVICES	8,106	21
Nuclear medicine	117	26
Laboratory	6,080	22
Chemistry	2,642	22
SMA-6	450	22
Hematology	1,231	21
Partial thromboplastin time	145	63
Prothrombin time	180	28
Platelets	142	25
Stat orders	795	43
Selected nursing	1,204	17
Vital signs	653	14
Weights	256	18
Fluid intake and output	295	23
Radiology	387	10
Chest x-ray film	197	9
Electrocardiogram	184	6

rated as clinically unnecessary for total services and for selected services. Tests itemized in the table were the most overused. A fifth of all 8,106 services reviewed were judged unnecessary. In all, 26% of nuclear medicine procedures, 22% of laboratory tests, 10% of radiologic procedures and 17% of three nursing services were judged to be unwarranted. Laboratory tests accounted for 78% of the unnecessary services. The single most overordered service was the partial thromboplastin time (63% unnecessary). Nearly half of *stat*-processing orders were felt to be unwarranted. Fluid intake and output was the most overordered nursing service audited. Reviewers rarely indicated that needed services were omitted.

Discussion

This study confirms substantial overuse of resources on the medicine service of one university teaching hospital. A fifth of services provided to medicine inpatients was judged to be clinically unwarranted. Although infrequently ordered, nuclear medicine procedures showed the greatest proportion of unnecessary orders (26%). Laboratory tests (22%) represented 78% of all unnecessary orders. Comparatively few radiologic procedures and electrocardiograms ordered were judged unnecessary: only 9% of chest radiographs were felt to be unwarranted.

Excessive use of nursing resources has received scant attention,[7] despite the fact that nursing represents the largest single hospital budget item. Our reviewers judged that a sixth of orders for selected nursing services was unwarranted.

Four factors, however, should be considered in interpreting these results. First, the research methods limit application of the results. Most important, patient cases were not selected randomly. The records chosen for review, however, did represent nearly half of all patients cared for by the house staff, suggesting that the results do reflect hospital service use for staff medicine patients.

Second, specific accepted standards for use do not exist for most of the hospital services available to physicians. Yet our application of general criteria yielded aggregate and specific levels of excessive ordering consistent with those found elsewhere.[1-3,8,9]

Third, although the broadest assessment of ordering to date, our study did not address larger clinical decisions, such as those determining lengths of hospital stay. Even greater costs may be cut by reducing excessively long stays.

Fourth, the study's setting was unique. Reviews were conducted by attending physicians in one teaching hospital. Although the results may not be directly applicable to other hospitals, the review techniques are. The reviews are easily conducted and highly acceptable to physicians.

Our reviews show that excessive use of hospital resources is substantial but not uniform across ancillary and nursing services. Such assessments guide the cost-cutting scalpel by identifying which services can be cut without diminishing quality of care. These results support the wisdom of identifying specific areas of excessive use through case reviews before embarking on potentially expensive cost-containment programs.[10]

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Commentary

The Most Cost-Effective and Quality-Effective Factor in Medical Care—Well-Trained, Conscientious Primary Care Physicians

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We are subject to a barrage of warnings about the rising costs of medical care and plans to bring costs down. I would like to make the case for a critical element in any system: a personal, primary care doctor for each person and family in the country. By primary care doctor I mean that physician whose help and advice is sought first, who is competent to care for 80% to 90% of illness problems and who is trained to understand prevention, psychodynamics and community resources. That doctor may be called pediatrician, family physician or general internist.

How can such a system be so cost-effective and quality-effective?

• *Teaching wellness and good health habits.* The personal doctor can instruct in diet, exercise, smoking and alcohol habits, relaxation, environmental hazards and accident prevention. He or she can follow up on the advice and its effect on health (cholesterol levels, for example) because there is a long-term ongoing physician-patient relationship. One of the most effective antismoking devices is the strong recommendations of a trusted personal physician.[1] A successful illness prevention program could save billions each year.[2]

• *A comprehensive, integrated, nonfragmented perspective* of the body and the mind saves much unnecessary diagnostic and therapeutic procedure. An everyday primary care practice has many illustrative examples: the persisting headache that the primary care physician recognizes as related to trouble at work and for which a casual visit to a clinic might result in an expensive CAT scan of the head; indigestion due to family tension at meals for which an upper gastrointestinal study might be ordered by a physician unfamiliar with the situation. This kind of doctor has the overview to safely "watch and wait" rather than rush to have laboratory or x-ray studies done.

• *A background of thorough initial history and physical and long-term continuing care.* The primary care physician often knows a patient well enough to diagnose and treat on the telephone accurately and safely, saving office visits and laboratory tests. When the emergency room calls that the patient is there with chest pain, the primary care physician often knows what a previous electrocardiogram showed, or that the patient has a habit of running to emergency rooms for costochondral junction pain and doesn't need another chest x-ray film. If there is not a primary care physician with some background information, the patient often gets a multitude of tests and perhaps an unnecessary hospital admission. There is clear evidence that patients benefit from such a continuing relationship.[3]

• *Training to care for many body systems.* It is not unusual for a patient to see her gynecologist for postmenopausal hot flashes, her orthopedist for osteoarthritis of the knee, her head and neck doctor for postnasal drip and her dermatologist for contact dermatitis. Except in unusual circumstances, a well-trained primary care physician can manage these problems as well as anyone and save the patient and the system many dollars for separate visits and consultations.

• *Understanding the family and psychodynamics.* It is estimated that 50% of doctor visits have a major psychologic component to the symptoms. Today's primary care physician is trained to recognize and treat most emotionally based illness and thereby save psychiatric fees, unwise laboratory tests and repeated visits to other specialists.

• *Trust and cooperation* built over years lead to better quality and cost-effective care. A trusted primary care physician is less likely to order tests for legal self-protection and also is more aware of the patient's financial status. This physician's commitment to the patient in a continuing relationship not only leads to referral to qualified specialists but also to the potential to influence consultants, when indicated, to modify their fees. When consultants disagree, the patient often turns to the primary care physician for the deciding advice that will include the social and psychologic as well as the medical and technical part of the equation. For example, when there is a question of the wisdom of resuscitative efforts, respirator use or tube feeding in a terminally ill patient, the primary care

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physician often knows the patient and family so well as to know their unspoken choice and to act accordingly.

I realize that I have presented an idealized picture. I also realize that primary care physicians who do not do their job well, who diagnose and treat beyond their competence or who ignore prevention and psychodynamics, can be cost- and quality-ineffective. The kind of physician I describe is, however, the goal of primary care training programs and is the kind of physician the programs are and have been producing.

Can we have this kind of medical care service with health care financing plans other than individual private practice? Is the group practice, HMO or PPO organizational system compatible with the personal physician, primary care concept? It is possible if it is really emphasized. There must be for each patient a person identifiable as "my doctor." Big organizations tend to disrupt the relationship of *direct obligation* of physician to patient and patient to physician. The insertion of many physicians, the clinic milieu, the third-party payor (including the government), the restriction of time available to spend with the patient, the emphasis on superspecialists and the limitations on which consultants can be used—all lead to a distortion of the kind of covenant I describe. This principle needs to be paramount: one patient, one physician, one goal.

How can we achieve the objective of a personal, primary care physician for everyone? We need to (1) expand support for primary care residency training and decrease support for the subspecialties already in overabundant supply, (2) rethink our compensation system so that primary care physicians have financial rewards at least approaching the other specialties[4] and (3) return to the era in which the poor receiving governmental support were part of "main stream" medical care, so that it would be financially feasible to service poor neighborhoods with primary care physicians.

Health care financing planners should know what a powerful force the primary care physician can be.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Physician as Assistant at Cataract Surgery

QUESTION:

If assistance is needed during the performance of cataract extraction, does the assistant need to have the training, experience and skills of a physician and surgeon? If so, what functions are performed by that assistant physician and surgeon?

OPINION:

In the opinion of the Scientific Advisory Panel on Ophthalmology, the assistance of a physician, trained in diseases and surgery of the eye, during intraoperative procedures such as cataract extraction is established medical practice. Recent advances in cataract surgery involving greater levels of technology and its attendant complexity have not diminished the need for such professional surgical assistance.

Among the considerations that place this in the patient's best interest are the following:

- The presence of a surgical assistant with the training, experience and skill of an ophthalmologist is optimal for many important steps during routine intraocular surgery, especially should emergencies occur such as hemorrhage, vitreous loss or anesthesia complications.
- Intraocular surgery is delicate and the initial procedure must be done with maximum skill and judgment. The assistant surgeon aids the surgeon to ensure the patient the best possible surgical results.
- On rare occasions, the surgical assistant may be required to complete an operation in the event the surgeon becomes disabled.

The functions carried out by an assistant at cataract extraction will vary depending on the technique used, the skill of the surgeon, the equipment required for the operation and the skill of the assistant.

Maizie's Problem

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

I sat next to the Duchess at tea
It was just as I feared it would be
Her rumblings abdominal
Were simply phenomenal
But everyone thought it was me!

Maizie, a woman of 63, sat across from me as we went over the results of her annual checkup. "You are perfectly healthy, Maizie," I said, "and the laboratory tests are all satisfactory. Is there anything else we need to talk about?"

"Well . . . No, I guess not," and she picked up her purse and prepared to leave. Then she paused, sat on the edge of her chair and said, "Oh yes, by the way, I do have one problem, but it's awfully hard for me to talk about. You see, I do have an awful lot of gas."

"I love peas and beans and lentil soup, but Doctor, whenever I indulge in them my stomach makes terribly embarrassing noises, to say nothing of the odor. Isn't there something I can do about that?"

Here I was faced with a common dilemma, a delicate and sensitive subject of great concern to many patients, yet seemingly so simple that any wise physician ought to be able to supply an explanation and a quick cure. Obviously, Maizie had confided to me a complaint of innermost concern. She expected me to provide a solution to her problem, one that would not require her to give up her peas, beans and lentil soup.

All too often our patients' complaint of "gas" is treated flippantly. Along with the piles, sore toes and dandruff, these various complaints, minor to us but major to patients, are too often passed over, even made the butt of crude jokes.

I think back to my undergraduate days when low-cost peas and beans provided daily sustenance at our fraternity house. At times my uncouth Greek brothers would vie to see who could expel the noisiest bolus of flatulence, and as a part of the evening's entertainment would put lighted matches to their posteriors, igniting the gaseous effluvient to produce magnificent puffs of blue flame. At that point in my embryonic premedical career I had not as yet learned about that mysterious substance—methane.

Not much help came from my professors in medical school. Oh, we were taught that flatulence resulted from intestinal fermentation involving complex proteins and indigestible carbohydrates. In order to avoid this fermentative flatulence, one professor with philosophical bent suggested that we follow the advice of the Greek astronomer, mathematician and philosopher Pythagoras: *"A fabis abstinetes."* Translated, his exhortation was, "Eat no beans!" This admonition for self-denial is of little comfort to our patients (or to us) who love our beans. But now there is new hope on the leguminous horizon. Modern science may have us on the brink of a discovery that might very well eliminate the music and malodor from a can of navy beans.

Working to perfect a cure, nutritional research workers have focused on the cause. To quote Stephen S. Hall writing in SCIENCE 84,[1] "The seeds of legumes—everything from chick-peas and lentils, to navy beans, string beans and soybeans—contain chains of sugar molecules called oligosaccharides. Some sugar chains, including such champion gas producers as raffinose, stachyose, and verbascose, pass relatively intact through the gastrointestinal tract."

"When these sugar chains reach the large intestine, anaerobic bacteria, which live peaceably in mammalian gut and metabolize food in the absence of oxygen, break down the oligosaccharides by fermentation. As metabolic by-products, these bacteria typically produce hydrogen, carbon dioxide, and, sometimes, methane." Hence the blue flame.

Because the gases are not absorbed, they must rumble and grumble down through the colon producing the "social discomfort" that Maizie complained of. (Our medical school professors taught us that the proper name for distressing gurgles was the wonderful onomatopoetic "borborygmus.")

The search for a cure of this noisy, malodorous malady takes us to Bombay, India, where V. S. Rao and U. K. Vakil,[2] working at the Bhabha Atomic Research Centre (after all, this is an explosive problem) are learning how to deflate the legumes that are a staple in the diet of Indians and of the people throughout the Third World. It's quite simple. After a preliminary soaking of the beans in distilled water they are then exposed to minute amounts of cobalt-60 radiation. Result: the two main culprits in flatulence production, stachyose and raffinose, become digestible, thereby reducing the gaseous fermentation.

Following this circuitous route we still have not found an answer to Maizie's problem. Our cautious Food and Drug Administration will not soon allow a can of beans to be labeled, "deflated and deodorized by cobalt-60." Until further research succeeds in bursting this borborygmic bubble we may have to say to Maizie, *a fabis abstinetes,* or just plain "eat no beans!"

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Information

Guidelines for Discontinuing Cardiopulmonary Resuscitation in the Emergency Department After Prehospital, Nonparamedic-Directed Cardiac Arrest

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PREHOSPITAL CARDIOPULMONARY RESUSCITATION (CPR) is increasingly used to treat sudden cardiac arrest. Previous studies have suggested that more than 20% of patients in such circumstances can be successfully resuscitated.[1-6] A substantial percentage of the reported survivors who are resuscitated in the field and brought to hospital have intrinsic cardiac activity.[1-11] The remaining patients, in whom field resuscitation attempts are unsuccessful, are brought to the emergency department for definitive therapy while still receiving active CPR. In this group, lengthy resuscitation is often attempted after arrival in the emergency department, although these patients are known to have a low probability of successful resuscitation and eventual hospital discharge.[5-8]

No accepted guidelines have been published that would enable physicians to decide when continued CPR in the emergency department is indicated or when it should be terminated. As a consequence, many victims of sudden death are undergoing expensive and unsuccessful attempts at CPR in the emergency department.

We analyzed 893 consecutive cases of prehospital resuscitation and conclude that the time from collapse to the initiation of CPR, the duration of active CPR and the cardiac rhythm on arrival can all be valuable discriminatory variables for predicting successful resuscitation in the emergency department. Attention to these factors can distinguish patients who should have aggressive CPR continued in the emergency department from those who will not benefit from such action.

Patients and Methods

A CPR training program has been in effect in Sacramento County (California) since 1976, and about 40,000 people each year have received basic CPR instruction from 1975 to the present according to the records of the American Red Cross Association and the American Heart Association of Sacramento. However, names were not cross-referenced to determine whether a participant had taken a basic CPR class twice.

Sacramento County includes a suburban and rural population of 754,000 that is 72% white, predominantly working and middle-class and 18% of which is older than 55 years. All prehospital CPR attempts from July 1979 to June 1981 in the county of Sacramento were reviewed. The cases were retrieved from the emergency department and hospital records of eight hospitals and were cross-referenced with the reports of the emergency medical technicians responsible for delivering the patients to hospital. Patients requiring CPR due to major trauma were excluded.

The records of emergency medical technicians (EMT) levels I and II were included in the study. EMT I care predominated in the first six months of the study and was gradually replaced with EMT II services. About 40% of the patients in the present series were initially treated by EMT I personnel. EMT I personnel were trained in administering basic CPR with bag-mask ventilation and in transporting patients receiving CPR to the nearest hospital emergency department. EMT II rescuers were further trained to assess vital signs, do CPR, interpret electrocardiographic monitoring data, carry out defibrillation and administer drugs intravenously, including sodium bicarbonate, epinephrine, lidocaine and atropine. Furthermore, they were trained to support ventilation either by a bag-mask system or by insertion of an esophageal obturator airway. EMT II personnel received remote voice direction from physicians based in predesignated emergency departments throughout the country. When indicated, defibrillation was done with either 200 or 300 joules per second. Mechanical assistance devices as a form of CPR were not used in this study.

In the sequence of resuscitation directed by a hospital-based physician, the EMT II personnel were ordered to establish an airway, insert an intravenous line and administer sodium bicarbonate and epinephrine before defibrillation if the cardiac arrest occurred before their arrival. If the arrest was witnessed by the EMT II rescuers, then immediate defibrillation was ordered. If defibrillation was successful, patients were further stabilized at the scene and then transported to hospital for definitive treatment and evaluation. When unsuccessful, CPR was continued during transport to hospital for further resuscitation or pronouncement of death.

For this study, successful resuscitation was defined as discharge from hospital of a patient who had had a documented prehospital cardiac arrest. Hospital course complications were ascertained from a review of hospital records. Neurologic impairment was considered severe when it necessitated total care or when it severely restricted independent function. Patients were judged as having no neurologic impairment when they could return to their prior way of life.

Patients with both witnessed and unwitnessed cardiac ar-

(Smith JP, Bodai BI: Guidelines for discontinuing cardiopulmonary resuscitation in the emergency department after prehospital, nonparamedic-directed cardiac arrest [Information]. West J Med 1985 Sep; 143:402-405)

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ABBREVIATIONS USED IN TEXT

CPR = cardiopulmonary resuscitation
EMT = emergency medical technician

rest were included in the study. A witnessed arrest was defined as an arrest observed either by sight or by an observer hearing the fall of the person. The time from arrest to initiation of CPR either by a lay bystander or by EMT personnel was recorded as estimated time between collapse and the initiation of CPR, except when they observed the arrest and began CPR immediately. Duration of prehospital CPR was defined and recorded by the rescuers as the time from the initiation of CPR until arrival at the emergency department. If resuscitation was successful at the scene (the patient had spontaneous pulse and cardiac activity), the duration of prehospital CPR was defined as the interval between initial cardiac arrest and cessation of manual CPR. The cardiac rhythm on arrival at the emergency department was obtained by review of the physician charts and nurses' notes. Most patients had sample rhythm strips in the charts, and these were verified by the authors against the stated impression. For 112 patients, none of whom survived, an adequate record of their cardiac rhythms on arrival at the emergency department could not be verified.

Results

During the study period, 893 patients with nontraumatic cardiac arrest were identified, 29 (3.2%) of whom survived long term (Figure 1). Of these, 20 (69.0%) were successfully resuscitated before arrival at the hospital and were eventually discharged. Only nine (31.0%) of the long-term survivors were undergoing active CPR on arrival at the emergency department. Five of the nine patients were resuscitated by EMT I personnel, whereas the other four were treated by EMT II personnel. Two of the nine patients had initial successful resuscitation and had been transported to the emergency department without active CPR but subsequently suffered a second cardiac arrest within three minutes of arrival. Seven patients (0.8%) were resuscitated on arrival at the emergency department after unsuccessful prehospital CPR. All these patients had ventricular fibrillation confirmed by electrocardiographic records.

A total of 79 patients (8.8%) was admitted to hospital, but 50 (63.3%) patients died during hospital stay. In all, 814 patients (90.9%) were declared dead in the emergency department after unsuccessful CPR. Of the 29 survivors, 5 (17%) suffered a severe neurologic deficit and required permanent institutional care. Only 24 of 893 patients (2.7%) resumed their prior activities when discharged from hospital.

The cardiac rhythms for all patients on arrival at the emergency department are shown in Figure 2. Asystole was the predominant rhythm, observed in 372 patients (47.6%) of the verifiable cases (N = 781). Asystole and bradyarrhythmias (agonal, idioventricular and electromechanical dissociation) were present in 511 patients (65.4%), 1 of whom survived. The cardiac rhythms for long-term survivors are also shown in Figure 2. A supraventricular rhythm, defined as atrioventricular conduction with a ventricular response, was present in 35 patients, 18 (51.4%) of whom were long-term survivors. These patients had spontaneous cardiac activity and were not receiving CPR. One patient (5.8%) of those with ventricular tachycardia and one patient (3%) of those with an idioventricular rhythm survived; however, each of these patients arrived with a palpable pulse and inherent cardiac activity. No patient with asystole or a bradyarrhythmia who arrived receiving active CPR survived. Nine patients (4.2%) of those with ventricular fibrillation were resuscitated.

The duration of prehospital CPR for patients resuscitated in the emergency department is shown in Table 1. Of the patients who had prehospital CPR for more than 30 minutes (34 minutes), only one survived. In another case, it was impossible to determine the exact duration of prehospital CPR, but that patient did not receive prolonged prehospital resuscitative efforts and was transported to the hospital quickly. The mean duration of prehospital CPR (under EMT II care) in our study was about 32 minutes.

The periods from cardiac arrest to the initiation of CPR for those patients who died in the emergency department are shown in Figure 3. The majority of arrests, occurring in 628 patients (70.3%), were unwitnessed or were associated with CPR done after more than five minutes had elapsed (Figure

TABLE 1.—*Duration of Prehospital CPR for Patients Resuscitated in the Emergency Department*

Time (min)	*Survivors (N)*
1-10	4
10-20	2
20-30	1
30-35	1
Unknown	1

CPR = cardiopulmonary resuscitation

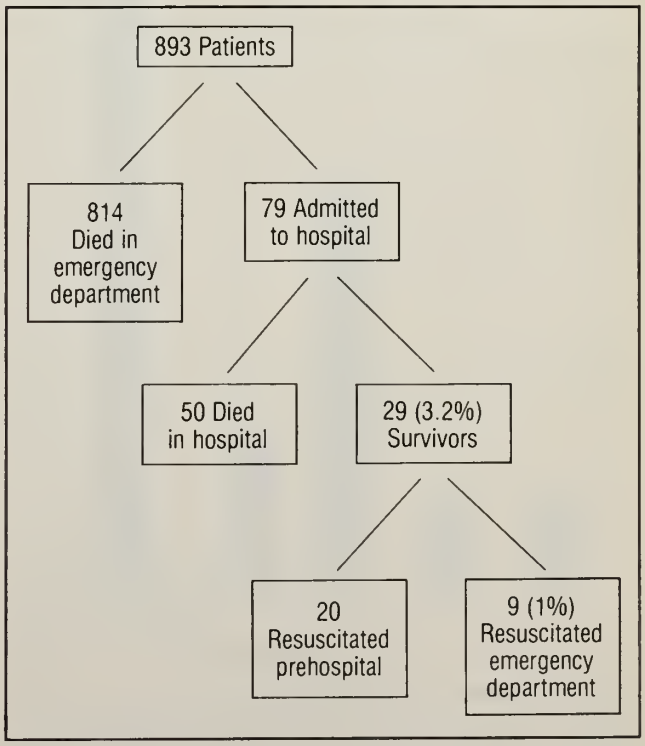

Figure 1.—Summary of nontraumatic cardiac arrest episodes in 893 patients.

4). Of the survivors resuscitated in the emergency department, all but one had witnessed arrests and had CPR initiated within five minutes after collapse. The only survivor of an unwitnessed arrest (who was resuscitated in the emergency department) suffered extensive neurologic injury resulting in only midbrain function at one-year follow-up.

Successful resuscitation before arrival at the hospital was unrelated to the age of the patients, except that no patient older than 84 years was resuscitated at the scene. No patient older than 77 years was successfully resuscitated in the emergency department; 180 patients (20.2%) were older than 75 years. Conversely, no patient younger than 20 years was resuscitated; 52 patients (5.8%) were younger than 20.

Comment

Viability after cardiac arrest is associated with the rapid initiation of CPR and the early institution of defibrillation. Previous reports have emphasized that CPR must be initiated within four minutes of collapse and defibrillation must be accomplished within eight minutes to achieve reasonable success.[1-5,9] Any delay greatly increases the risk of death. Since 1970, many communities have begun EMT and paramedic programs, and training lay personnel in CPR techniques has been enthusiastically attempted. However, the crucial variable—a trained, responsive population—has been more difficult to achieve.[10] As a consequence, many of the victims of sudden death have CPR initiated only after a considerable delay. Many patients who might possibly benefit from CPR must await the arrival of trained professional rescuers, and most are brought to hospital in a physiologic state not conducive to resuscitation.[1-8] Although guidelines have been proposed, none are currently accepted that would enable an attending physician to distinguish patients who might benefit from continued CPR from those who are clinically dead on arrival.[11] CPR as currently practiced within emergency departments is costly, and the technique should be applied in a rational manner.

Patients who were successfully resuscitated in our series had characteristics similar to patients rescued in other studies. They had prompt institution of CPR and early definitive care; more important, they had a rhythm amenable to defibrilla-

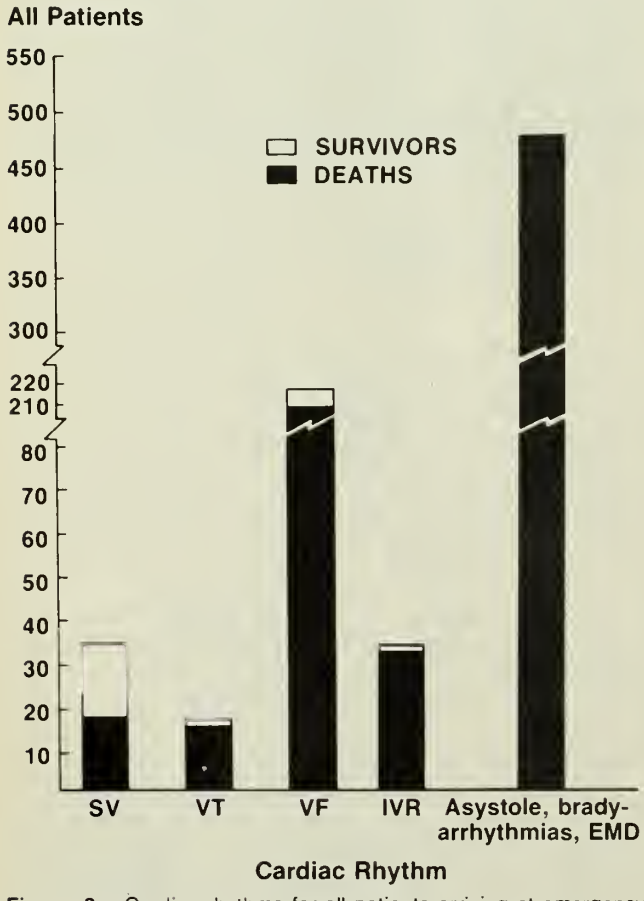

Figure 2.—Cardiac rhythms for all patients arriving at emergency department after prehospital cardiopulmonary resuscitation. SV = supraventricular rhythm with spontaneous cardiac activity, VT = ventricular tachycardia, VF = ventricular fibrillation, IVR = idioventricular rhythm, EMD = electromechanical dissociation

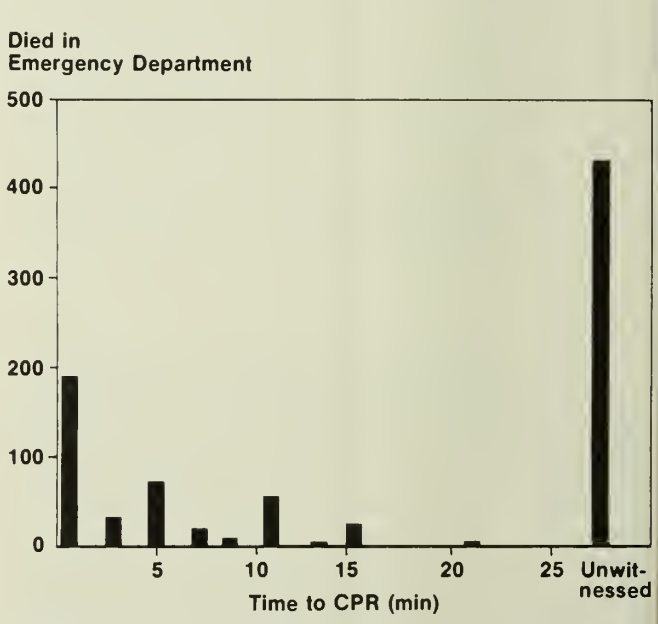

Figure 3.—Time from collapse until initiation of cardiopulmonary resuscitation (CPR).

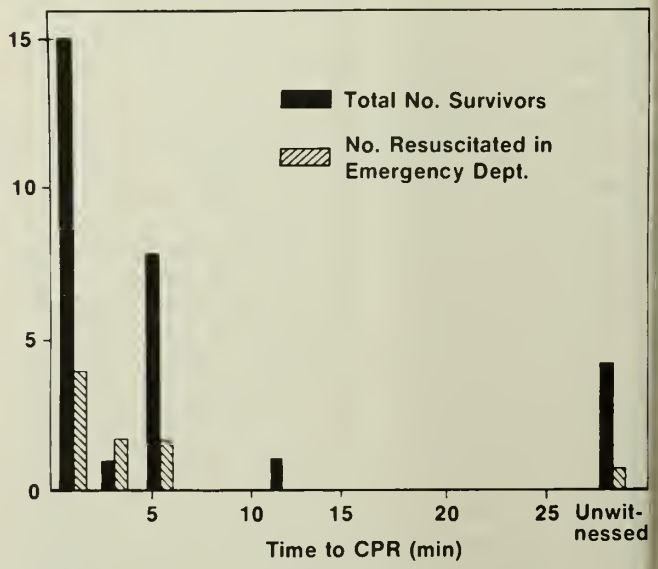

Figure 4.—Time from collapse until initiation of cardiopulmonary resuscitation (CPR) for patients resuscitated at scene of cardiac arrest and for those resuscitated in emergency department.

tion—ventricular fibrillation, ventricular tachycardia or both.[9]

Those who did not survive in this series had distinct characteristics as well. The initiation of CPR was delayed and CPR was prolonged. In addition, their cardiac rhythms were those characteristically not amenable to defibrillation.[1-3] The first cardiac rhythm recorded in the hospital after unsuccessful prehospital CPR discriminated between survivors and nonsurvivors. All survivors resuscitated in the emergency department had ventricular fibrillation on arrival at the hospital. Nearly 70% of the patients were asystolic or had a bradyarrhythmia without an associated pulse when they arrived at the emergency department. Previous studies in which the initial rhythm at the scene of cardiac arrest has been analyzed have confirmed a poor success rate in patients with asystole or bradyarrhythmic patterns.[1-3]

Analysis of the cardiac rhythm on arrival at the emergency department after an extensive attempt at prehospital CPR distinguishes our study from previous series. Asystole or bradyarrhythmias are an ominous sign, and current therapeutic techniques do not appear useful in reviving these patients.

An unwitnessed cardiac arrest is associated with a high mortality rate also.[2] In our series, an unwitnessed arrest occurred in most patients, only five of whom survived, four who were resuscitated before they arrived at the hospital. Of nine survivors who required hospital resuscitation, an unwitnessed arrest occurred in only one, who did not receive extensive prehospital care but was promptly transported to hospital. Thus, patients with an unwitnessed arrest who are not resuscitated at the scene constitute an apparently unsalvageable group. Patients with an unwitnessed arrest who did not respond to the initial resuscitation could not be revived in the emergency department.

The duration of prehospital CPR required also correlated with survival. Only one patient was resuscitated after 30 minutes of CPR at the scene of the cardiac arrest. CPR, which at best achieves 35% of normal blood flow, appears to be decreasingly effective with time.[12-16] CPR administered in the street or in the back of a moving ambulance is even less effective in supporting circulation. The duration of prehospital CPR appears to be inversely proportional to the chance of survival.

Although the poor results from this study have several causes, two technical factors probably contributed to the outcome. Successful prehospital resuscitation requires adequate prehospital ventilatory management. In most series of reported success with prehospital CPR, endotracheal intubation has been the ventilatory method used. Many communities, however, do not use this technique. In our series, the esophageal obturator airway was used, a device that has not been shown to provide adequate ventilation.[17] Thus, we could not ensure optimum prehospital ventilation for our victims of cardiac arrest, and our results may reflect this fact.

Second, early defibrillation was not universally applied in our series. Previous reports[2,3] have shown the necessity, to ensure successful prehospital CPR, of promptly defibrillating, when appropriate.

On the basis of our data, however, certain criteria can be established to determine the necessity for continued CPR by emergency department personnel for victims of prehospital cardiac arrest. These criteria would apply in communities not serviced by paramedics or when paramedics do not have the option of inserting an endotracheal tube in prehospital resuscitative efforts to revive patients who are not hypothermic or victims of cold water drowning.

In an unwitnessed arrest, when asystole or a bradyarrhythmia not associated with spontaneous cardiac activity is noted and when the patient has had the benefit of EMT II or paramedic-directed CPR efforts at the scene, no further action is deemed necessary.

These guidelines would reduce hospital-based CPR attempts more than half, in our experience, without jeopardizing any potentially salvageable patient. All patients could be rapidly classified from information obtained from the rescuers on arrival at the emergency department and from an electrocardiogram.

Conclusion

Rigorous CPR should be done in the following circumstances: when CPR has been initiated promptly after collapse, when there has been no attempt at prehospital defibrillation or definitive resuscitation and when the patient has a rhythm amenable to defibrillation (ventricular tachycardia or ventricular fibrillation).

Prolonged CPR is almost invariably futile. As a nation, we have devoted time and resources to improving cardiopulmonary resuscitation; we need to recognize its limitations.

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In Memoriam

California Medical Association

BREGER, SAMUEL, San Francisco. Died February 17, 1985, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1935. Licensed in California in 1935. Dr Breger was a member of the San Francisco Medical Society.

CASTRO, AMOS J., JR., San Francisco. Died in May 1985 in San Francisco, aged 70. Graduate of Louisiana State University School of Medicine, New Orleans, 1942. Licensed in California in 1943. Dr Castro was a member of the San Francisco Medical Society.

COFFROTH, LEROY WARD, Sacramento. Died May 24, 1985, in Sacramento of cancer, aged 63. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1950. Licensed in California in 1964. Dr Coffroth was a member of the Sacramento-El Dorado Medical Society.

COOPER, SAMUEL S., Los Angeles. Died March 5, 1985, aged 74. Graduate of the Chicago Medical School, 1939. Licensed in California in 1950. Dr Cooper was a member of the Los Angeles County Medical Association.

DUBOIS, EDMUND L., Los Angeles. Died February 2, 1985, of cancer, aged 61. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1946. Licensed in California in 1947. Dr Dubois was a member of the Los Angeles County Medical Association.

GREER, VERNON E., JR, Sacramento. Died May 29, 1985, in Lodi, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr Greer was a retired member of the Sacramento-El Dorado Medical Society.

HOLLIFIELD, WILLIAM C., Sacramento. Died April 26, 1985, in Sacramento, aged 65. Graduate of Medical College of South Carolina, 1943. Licensed in California in 1966. Dr Hollifield was a member of the Sacramento-El Dorado Medical Society.

JOHANSON, RAYMOND R., Lafayette. Died April 10, 1985, in Sun City, Arizona, aged 77. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr Johanson was a retired member of the Alameda-Contra Costa Medical Association.

JOHNSON, LESTER J., San Jose. Died May 4, 1985, in San Jose, aged 86. Graduate of the University of Michigan Medical School, Ann Arbor, 1925. Licensed in California in 1946. Dr Johnson was a retired member of the Santa Clara County Medical Society.

MAPES, RUSSELL W., Los Angeles. Died April 3, 1985, in Seattle, aged 80. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1931. Licensed in California in 1934. Dr Mapes was a retired member of the Los Angeles County Medical Association.

MARQUETTE, MARTIN L., Vallejo. Died November 5, 1984, aged 98. Graduate of the Indiana University School of Medicine, Bloomington-Indianapolis, 1917. Licensed in California in 1921. Dr Marquette was a member of the Solano County Medical Society.

MILLIKEN, JOSEPH HUNT, Oakland. Died February 27, 1985, in Oakland, aged 82. Graduate of McGill University Faculty of Medicine, Montreal, 1932. Licensed in California in 1933. Dr Milliken was a retired member of the Alameda-Contra Costa Medical Association.

NOECKER, F. PATIENCE, Fall River Mills. Died March 26, 1985, of injuries received in a motorcycle accident in Nepal, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1951. Licensed in California in 1951. Dr Noecker was a member of the Shasta-Trinity County Medical Society.

PAUL, SAMUEL E., Napa. Died May 4, 1985, in Napa, aged 74. Graduate of Boston University School of Medicine, 1937. Licensed in California in 1969. Dr Paul was a retired member of the Napa County Medical Society.

ROEN, PAUL B., Hollywood. Died February 10, 1985, in Los Feliz Hills, aged 95. Graduate of Los Angeles Medical Department, University of California, 1914. Licensed in California in 1916. Dr Roen was a retired member of the Los Angeles County Medical Association.

VERTEL, ROBERT MICHAEL, Walnut Creek. Died April 10, 1985, of pancreatic cancer, aged 48. Graduate of the University of Illinois College of Medicine, Chicago, 1961. Licensed in California in 1966. Dr Vertel was a member of the Alameda-Contra Costa Medical Association.

WHITTAKER, THOMAS W., Los Angeles. Died October 12, 1984, aged 79. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Dr Whittaker was a retired member of the Los Angeles County Medical Association.

New Mexico Medical Society

EVANS, LELAND S., Las Cruces. Died May 8, 1985, aged 76. Graduate of the University of Texas School of Medicine, Galveston, 1933. Licensed in California in 1935. Dr Evans was an Emeritus member of the Dona Ana County Medical Society.

O'MALLEY, ANTHONY F., Roswell, Died June 11, 1985, aged 35. Graduate of the University of Arizona College of Medicine, Tucson, 1975. Licensed in New Mexico in 1979. Dr O'Malley was a member of the Chaves County Medical Society.

YOUNG, ALMA L., Albuquerque. Died April 17, 1985, aged 60. Graduate of the University of Texas School of Medicine, Galveston, 1949. Licensed in New Mexico in 1974. Dr Young was a member of the Albuquerque & Bernalillo County Medical Society.

Utah State Medical Association

ENGLERT, EDWIN J., Salt Lake City. Died June 2, 1985, in Salt Lake City, aged 58. Graduate of Columbia University College of Physicians and Surgeons, New York, 1949. Licensed in Utah in 1955. Dr Englert was a member of the Salt Lake County Medical Society.

HORNE, LYMAN MERRILL, Salt Lake City. Died May 2, 1985, in Salt Lake City, aged 88. Graduate of Columbia University College of Physicians and Surgeons, 1920. Licensed in Utah in 1924. Dr Horne was a member of the Salt Lake County Medical Society.

SHARP, SCOTT C., Salt Lake City. Died May 9, 1985, in Salt Lake City, aged 60. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1960. Licensed in Utah in 1949. Dr Sharp was a member of the Salt Lake County Medical Society.

Washington State Medical Association

BARR, ROBERT E., Seattle. Died in February 1985, aged 57. Graduate of Baylor College of Medicine, Houston, 1953. Licensed in Washington in 1954. Dr Barr was a member of the King County Medical Society.

BIRKELAND, IVAR W., SR., Bellevue. Died in March 1985, aged 87. Graduate of Kongelige Frederiks Universitet Medisinke Fakultet, Oslo, 1924. Licensed in Washington in 1926. Dr Birkeland was a retired member of the King County Medical Society.

BROWN, WALTER S., Seattle. Died April 7, 1985, in Seattle, aged 78. Graduate of the University of Illinois College of Medicine, Chicago, 1932. Licensed in Washington in 1932. Dr Brown was a retired member of the King County Medical Society.

DAVIES, ROBERTS J., Seattle. Died January 23, 1985, in Seattle, aged 75. Graduate of the University of Minnesota Medical School, Minneapolis, 1933. Licensed in Washington in 1947. Dr Davies was a retired member of the King County Medical Society.

DOWNIE, KENNETH ERNEST, Seattle, Died May 6, 1985, aged 69. Graduate of the University of Tennessee College of Medicine, Memphis, 1944. Licensed in Washington in 1947. Dr Downie was a retired member of the King County Medical Society.

ELLIS, FRED A., Seattle. Died April 4, 1985, aged 75. Graduate of the University of Minnesota Medical School, Minneapolis, 1937. Licensed in Washington in 1949. Dr Ellis was a retired member of the King County Medical Society.

GRINSTEIN, ALEXANDER, Seattle. Died December 24, 1984, aged 84. Graduate of Northwestern University Medical School, Chicago, 1923. Licensed in Washington in 1924. Dr Grinstein was a retired member of the King County Medical Society.

GUNN, ELIZABETH MCCAIN, Seattle. Died September 29, 1984, in Seattle, aged 86. Graduate of the University of Oregon Medical School, Portland, 1927. Licensed in Washington in 1929. Dr Gunn was a retired member of the King County Medical Society.

HADFIELD, DALE, Bremerton. Died April 6, 1985, in Puyallup, aged 68. Graduate of the University of Louisville School of Medicine, Louisville, 1942. Licensed in Washington in 1955. Dr Hadfield was a member of the Kitsap County Medical Society.

HILLERY, DANA R., Issaquah. Died January 8, 1985, in Seattle of lung disease, aged 80. Graduate of the University of Toronto Faculty of Medicine, Toronto, 1931. Licensed in Washington in 1932. Dr Hillery was a retired member of the King County Medical Society.

HOLLOWAY, JACKSON K., Seattle. Died May 1, 1985, in Seattle, aged 90. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1920. Licensed in Washington in 1928. Dr Holloway was a retired member of the King County Medical Society.

JOHNSON, PHILLIP O. C., Seattle. Died November 26, 1984, in Seattle, aged 76. Graduate of Rush Medical College, Chicago, 1932. Licensed in Washington in 1936. Dr Johnson was a retired member of the King County Medical Society.

LARSON, CHARLES P., Tacoma. Died October 4, 1984, in Tacoma, aged 74. Graduate of McGill University Faculty of Medicine, Montreal, 1936. Licensed in Washington in 1937. Dr Larson was a retired member of the Medical Society of Pierce County .

LASHER, EARL PARSONS, Seattle. Died in November 1984 in Seattle of heart disease, aged 74. Graduate of Cornell University Medical School, New York, 1934. Licensed in Washington in 1944. Dr Lasher was a retired member of the King County Medical Society.

MCKAY, DONALD F., Washougal. Died in May 1985, aged 60. Graduate of the University of Washington School of Medicine, Seattle, 1950. Licensed in Washington in 1951. Dr McKay was a member of the Clark County Medical Society.

OHMAN, ALBERT CARL, Seattle. Died November 8, 1984, in Seattle, aged 81. Graduate of the University of Colorado School of Medicine, Denver, 1932. Licensed in Washington in 1933. Dr Ohman was a retired member of the King County Medical Society.

SMITH, JOHN EDWARD, Seattle. Died May 14, 1985, in Seattle, aged 63. Graduate of the Creighton University School of Medicine, Omaha, 1946. Licensed in Washington in 1950. Dr Smith was a retired member of the King County Medical Society.

SULIS, ERNEST NOEL, Longview. Died February 7, 1985, in Longview, aged 85. Graduate of McGill University Faculty of Medicine, Montreal, 1923. Licensed in Washington in 1928. Dr Sulis was a retired member of the Cowlitz-Wahkiakum County Medical Society.

VAN ACKEREN, EUGENE G., Seattle. Died December 10, 1984, in Seattle, aged 67. Graduate of the University of Nebraska College of Medicine, Omaha, 1942. Licensed in Washington in 1958. Dr Van Ackeren was a retired member of the King County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

MEDICAL MALPRACTICE—A PREVENTIVE APPROACH—William O. Robertson, MD, Professor, Department of Pediatrics, University of Washington; Head, Washington State Medical Association Risk Management Program, and Director of the Quality Assurance Program, Children's Orthopedic Hospital, Seattle. University of Washington Press, Seattle, WA 98105, 1985. 222 pages, $20.

Probably no issue is currently of greater concern to physicians than professional liability and malpractice. The demoralizing effects on physicians, the real or perceived injury to patients, the potential impact on the availability of needed care and the cost of the liability situation ought to be a concern of everyone.

The medical profession, acutely realizing the sinister effects of professional liability, is committed to an equitable resolution of the growing crisis. Much needs to be done in social, judicial and political arenas, but, unfortunately, many physicians tend to believe it is purely the system that is flawed and needs correcting. Bill Robertson, MD, shows in a convincing manner that much can and should be done within the profession.

Through well-documented cases and piercing analysis, Dr Robertson clearly shows physician responsibility for reducing acts of negligence or the appearance thereof. Reassuring is his comment, "Individual instances of negligence were obvious, but no pattern of unprofessional behavior developed." Not so reassuring was the demonstration, based on closed cases reviewed in the state of Washington, that 24% had deficient informed consent, that 20% related to improper administration or inappropriate prescription of drugs and that 66% of the cases resulted from administrative or managerial shortcomings as opposed to knowledge or judgment. Quite rightfully, he laments, "We know what to do, it just does not get done."

With an easy yet penetrating style, multiple actual cases are presented and discussed as to their magnitude of occurrence. Each chapter contains single "What can you do?" portions which if studied and implemented carefully could go a long way toward reducing malpractice actions.

Quite clearly the "focus has been on those issues perceived as able to be influenced by changes in physician individual or collective behavior." Every malpractice action begins as a physician-patient encounter. Those who believe nothing needs to be done within the profession, and those who want to know what can be done, all need to read this book.

JAMES S. TODD, MD
President
Physician Insurers Association of America
Senior Deputy Executive Vice President
American Medical Association
Chicago

* * *

PREGNANCY, DIABETES AND BIRTH—A MANAGEMENT GUIDE—Dorothy Reycroft Hollingsworth, MD, Professor of Reproductive Medicine and Medicine, University of California, San Diego. Williams & Wilkins, 428 E. Preston St., Baltimore, MD 21202, 1984. 159 pages, $34.00

This book is a valuable, complete reference for pregnancy in diabetic women. It would be valuable for residents in family medicine as well as obstetrics and pediatrics. It is also potentially useful in any practice where pregnant diabetic patients are managed. Some surprises occur for this reviewer, including a close differentiation between type I and type II diabetes, as well as more attention to gestational diabetes than was heretofore recommended. I was surprised to see a correlation between poor diabetic control in the first trimester of pregnancy and developmental anomalies. With the new gadgetry available for home testing of blood sugars, the old Tes-Tape method is far outdated. Overall, such anxiety is created by this document that I believe I would be unwilling to accept a diabetic pregnant patient, as I have in past years.

My only criticism is the recommendation that all such patients be referred to major medical centers which are far away from my hometown and many others in the United States. One other slight criticism is that there is no suggestion that diabetic mothers probably should limit the size of their families; I think this would be a reasonable recommendation for any attending physician if the patient were a problem diabetic.

This book is definitely recommended.

J. JEROME WILDGEN, MD
Kalispell, Montana

* * *

THE CLINICAL NEUROSCIENCES—Volume IV, NEURORADIOLOGY—Editor: Roger N. Rosenberg, MD, Professor of Neurology and Physiology, Chairman, Dept of Neurology, University of Texas Health Science Center at Dallas, Southwestern Medical School, Chief, Neurological Services, Parkland Hosp.tal and Children's Medical Center, Dallas; Associate Editor: E. Ralph Heinz, MD, Professor of Radiology (Neuroradiology), Duke University School of Medicine, Durham, NC; with 19 contributors. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 968 pages, $150.00.

The Clinical Neurosciences is edited by Dr Roger N. Rosenberg and the series of five volumes represents an attempt to integrate new ideas and developments in the disciplines of neurology, neurosurgery, neuropathology, neuroradiology and neurobiology. Volume 4, entitled *Neuroradiology*, is edited by Dr E. Ralph Heinz and includes 21 chapters from 19 contributors. This is an outstanding work and indeed represents a major contribution to the neurosciences. The book provides a comprehensive overview of neuroradiological techniques and describes how these techniques are used diagnostically. Diseases of the central nervous system and their clinical and pathological manifestations are described with great skill and clarity. The cranium and brain are considered in chapters 1 to 12 and the spinal cord in chapters 13 to 21. Most of the radiographs and line drawings are outstanding and illustrate the techniques and pathologic conditions very satisfactorily. Occasionally, the CT pictures are not optimally reproduced and, in such cases, the pathology is difficult to appreciate. This volume is a welcome addition to the neuroradiological literature and updates several established references including *Diagnostic Neuroradiology* by Taveras, *Introduction to Neuroradiology* by Peterson and Kieffer and *Neuroradiology* by Burrows and Leeds. It is recommended enthusiastically.

NICOLE-FR. BOLENDER, MD
Department of Radiology
University of Washington
Seattle

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References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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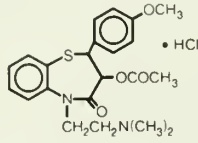

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In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CAROIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LOH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CAROIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CAROIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Oegree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LO_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NOC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NOC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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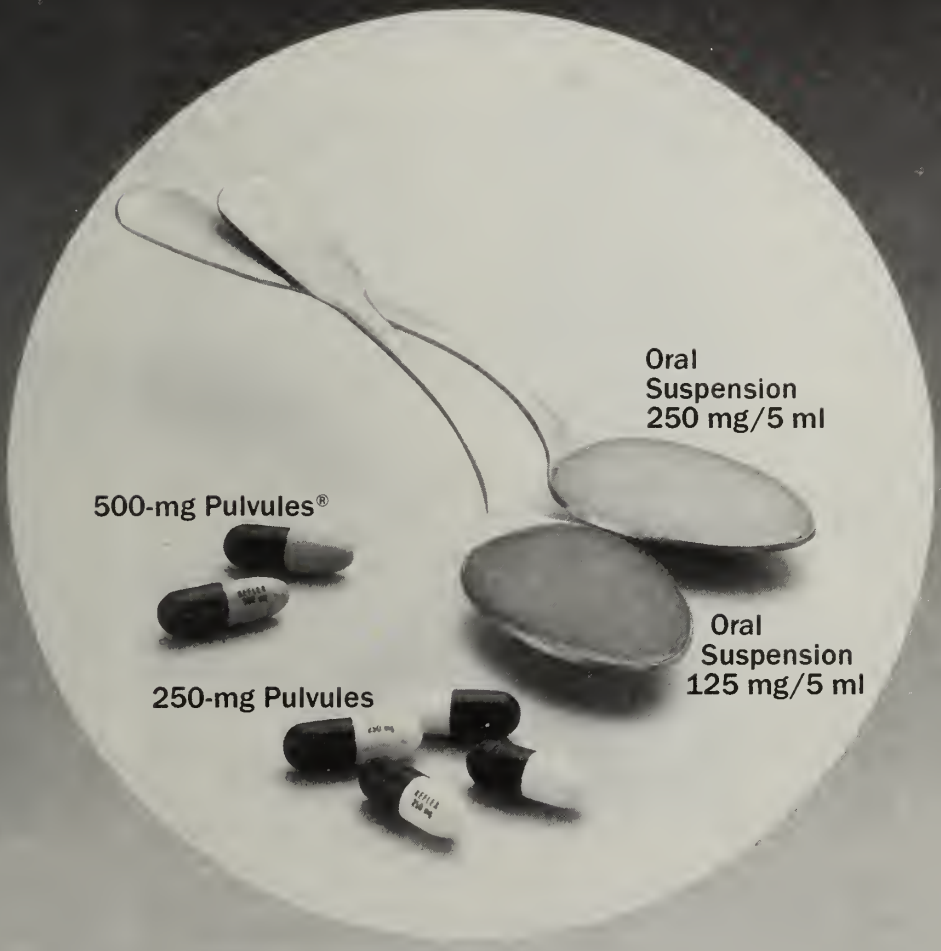

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(Continued from Page 326)

October 25-27—**9th American Imagry Conference.** International Imagry Association at Ambassador Hotel, Los Angeles. Friday-Sunday. Fee: $120, $140 after October 18. Contact: International Imagry Association, PO Box 1046, Bronx, New York 10471 (Judy Marks).

November 2—**Structural Family Therapy Beyond the Basics.** Mental Research Institute at Palo Alto. Saturday. 6 hrs. Fee: $75. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 4-8—**Couple and Family Therapy Conflict and Change.** Mental Research Institute at Palo Alto. Monday-Friday. 15 hrs. Fee: $180. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 9—**Structural and Strategic Family Therapies: A Dialogue.** Mental Research Institute at Palo Alto. Saturday. 6 hrs. Fee: $75. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. 321-3055.

November 22-24—**Guided Imagery for Clinicians.** Institute for the Advancement of Human Behavior at Honolulu, Hawaii. Friday-Sunday. Fee: $245-$350. Contact: IAHB, 4370 Alpine Rd., Ste. 205, Portola Valley 94025. (415) 851-8411.

RADIOLOGY

October 3-5—**3rd Biannual Symposium in Cardiac Imaging.** The Institute for Medical Studies at Hotel Meridien, San Francisco. Thursday-Saturday. 18 hrs. Contact: Kim Stroich, IMS, 20131 Town Center Drive, #215, Laguna Nigel, CA 92677. (714) 494-4499.

October 19-20—**Head and Neck Radiology: Advanced Techniques in Diagnostic Imaging.** UCSF at Hyatt Regency, San Francisco. Saturday-Sunday. 12 hrs. $175-$275.

October 19-20—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Hegency, San Francisco. Saturday-Sunday.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency, San Francisco. Monday-Friday. 31 hrs. $375-$475.

October 28-November 1—**10th Annual San Diego Postgraduate Radiology Course.** UCSD at San Diego. Monday-Friday. $425. Contact: Mary J. Ryals, PO Box 610103, Dallas Fort Worth Airport, TX 75261. (214) 659-9590.

November 4-8—**Diagnostic Radiology Seminars.** UCSF at Maui Marriott Resort, Hawaii. Monday-Friday. Fee: $375-$475. Contact: UCSF.

SPORTS MEDICINE

October 24-25—**Sports Medicine Hawaii: International Endurance, Sports and Fitness Symposium II.** UCI at Sheraton Royal Waikoloa, Kona, HI. Thursday-Friday. 16 hrs. $90-$240. Contact: J. Massimino, MD, 896 Town and Country Office Park, Orange, CA 92668. (714) 989-3432.

October 24-25—**Campbell's Endurance Sport and Fitness Symposium.** UC Irvine at Kona, Hawaii. Thursday-Friday. 16 hrs. Fee: $240. Contact: J. Massimino, MD, 896 Town and Country Office Park, Orange 92668. (818) 999-3432.

November 1-3—**Sports Medicine and Outpatient Orthopedics for the Primary Care Physician.** Continuing Medical Education Association at Hotel Intercontinental San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

November 1-6—**Women's Sports Medicine Update.** School of Medicine at Hyatt Regency, Monterey. Friday-Wednesday. Contact: Office of Continuing Medical Education, School of Medicine, UC Davis, 2701 Stockton Blvd., Sacramento 95817. (916) 453-5390.

SURGERY

September 4-7—**Superficial Anatomy and Cutaneous Surgery for Dermatologists.** UCSD at San Diego. Wednesday-Saturday. 22.5 hrs. Contact: UCSD.

September 18-21—**A Cementless Revolution in Joint Replacement 1985.** UCLA Extension at Los Angeles. Wednesday-Saturday. 27 hrs. Fee: $100-$475. Contact: UCLA Extension, PO Box 24901, Los Angeles. (213) 825-7186.

September 21-22—**Annual Scientific Symposium: Controversies in Surgery.** International College of Surgeons, Southern California Division, at Las Vegas Hilton, Las Vegas, NV. Saturday-Sunday. 3 hrs. Contact: (213) 483-1581, ext. 251.

October 4—**One Day Dermatologic Office Procedures.** Continuing Medical Education Associates at Lkona Kai Club, San Diego. Friday. 7 hrs. Fee: $175. Contact: J. Shiller, CMEA PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-20—**Anterior Cruciate Ligament.** Memorial Medical Center at Long Beach. Saturday-Sunday. 10.5 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

October 19-26—**7th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott Hotel, HI. Saturday-Saturday. 36 hrs. $875.

(Continued on Page 414)

Utah State Medical Association

Annual Meeting

Westin Hotel Utah, Salt Lake City
September 25-27, 1985

Forum on Medical Issues

Thursday, September 26, 1985 2:00-5:00 p.m.

Government

Carolyne K. Davis, RN, PhD

Administrator of the Health Care Financing Administration (HCFA). Dr Davis oversees the functions of the Medicare and Medicaid programs. HCFA helps to finance health care services for 50 million poor, elderly and disabled Americans with a budget over $90 billion in fiscal year 1985.

Medical Ethics

Ernlé W. D. Young, PhD

Chaplain at the Stanford University Medical Center, Dr Young is a senior lecturer on medical ethics. With a worldwide perspective, Dr Young is well informed on ethical conflicts currently facing medicine.

Hospitals

Scott S. Parker, MHA

Executive officer and president for Intermountain Health Care, Mr Parker is also chairman of the Board of Trustees for the American Hospital Association and past chairman of Associated Health Systems.

Physicians

Joseph F. Boyle, MD

Immediate past president of the American Medical Association and executive director for ASIM, Dr Boyle was chairman for the Health Agenda for the American People, a three-year study on health policy. A knowledgeable and captivating speaker, Dr Boyle brings to the forum the perspective of physicians and the challenges they will face in the modern medical marketplace.

Computer Seminars

Friday, September 27, 1985 9:00 a.m.-5:00 p.m.

The USMA computer seminars will provide cutting-edge information for physicians who are potential, new or experienced users.

Scientific Program

Friday, September 27, 1985 9:00 am-12:00 Noon

This exceptional half-day course provides a medical update on heart and vascular disease.

Private Practice Marketing Strategies

Friday, September 27, 1985
1:30-4:30 pm

Registration: No registration fee for USMA members; Nonmembers $50
For further information or registration material,
please contact Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. Telephone (801) 355-7477.

(Continued from Page 412)

November 1-4—**Cyriax Approach to Orthopaedic Medicine.** Thomas A. Dorman, MD, at San Luis Obispo. Friday-Monday. 24 hrs. Fee: $420. Contact: Thomas A. Dorman, MD, 1041 Murray Ave., San Luis Obispo 93401. (805) 544-3126.

November 2—**Spinal Cord Injury Update.** UCD at Sacramento. Saturday. Contact: Office of Continuing Medical Education, School of Medicine, 2701 Stockton Blvd., Sacramento 95817. (916) 453-5390.

OF INTEREST TO ALL PHYSICIANS

September 18-19—**53rd Annual Fall Symposium.** American Heart Association at Wilshire Blvd. Hilton, Los Angeles. Wednesday-Thursday. 13 hrs. Fee: $100-$185. Contact: Marianne Joyce, AHA, Greater Los Angeles Affiliate. (213) 385-4231.

September 18-20—**Adolescent and Family Treatment: An Investment for the Future.** The McDonald Center for Alcoholism and Drug Addiction Treatment Center of Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Wednesday-Friday. Fee: $190. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 454-6222.

September 19-22—**International Sex Research Conference/1985 Annual Conference.** The Society for the Scientific Study of Sex, Inc. at Holiday Inn Embarcadero, San Diego. Thursday-Sunday. 14 hrs. Contact: Dwight Dixon, PhD, PO Box 9902, San Diego, 92109. (619) 276-3616.

September 23-27—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD. Monday-Friday. 13-33 hrs. Fee: $215-440.

September 26-28—**1985 Pacific Occupational Safety and Health Conference** at Le Baron Hotel, San Jose. Thursday-Saturday. Contact: Duke Hughes, POSH '85, PO Box 4420, Santa Clara, CA 95054. (408) 988-1111.

September 27-28—**40th Annual Merritt Hospital Medical Staff Seminar: Medicine, 1985.** Samuel Merritt Hospital at Kaiser Center and Merritt Hospital, Oakland. Friday-Saturday. 10 hrs. Fee: $20. Contact: Patricia R. Napp, Med. Staff Support Services, Merritt Peralta, Hawthorne Ave. & Webster St., Oakland, CA 94609. (415) 655-4000.

September 28-29—**The Skin From A to Z.** UCSF at Holiday Inn, Napa Valley. Saturday-Sunday.

September 29-October 2—**Symposium on Prevention of Osteoporosis.** University of Hawaii at Westin Ilikai Hotel, Honolulu. Sunday-Wednesday. 13.5 hrs. Fee: $300. Contact: Dr Philip Ross, Osteroporosis Center, Kuakini Medical Center, 347 N. Kaukini St., Honolulu, HI 96817. (808) 547-9578.

October 4—**One Day Dermatology Office Procedures.** Continuing Medical Education Associates at Kona Kai Club, San Diego. Friday. 7 hrs. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

October 4-6—**29th Annual Western Occupational Health Conference.** California Society of Internal Medicine at Marriott Hotel, Irvine. Friday-Sunday. Contact: Joe Donovan c/o WOMA, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 6—**One Day Dermatology and Dermatology Office Procedures.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. 7 hrs. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

October 7-9—**Basic Hypotherapy Principles and Applications.** MRI Workshops at Palo Alto. Monday-Wednesday. 6 hrs. Fee: $75. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 7-11—**Brief Therapy. MRI Workshops at Palo Alto.** Monday-Friday. 15 hrs. Fee: $195. Contact: Training Program Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 12—**Recent Advances in the Diagnosis, Understanding, and Treatment of Chemical Dependency.** La Vina Auditorium Huntington Memorial Hospital at Pasadena. Saturday. 6 hrs. Fee: $60. Contact: Ingleside Hospital Public Relations Department (818) 571-4851.

October 16—**Alcohol and Drug Symposium.** Southern California Permanente at Pasadena Hilton Hotel, Pasadena. Wednesday. Contact: Judy Harrison, Dept. of Clinical Services, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 17-20—**Clinical Biofeedback Certificate Program.** UCLA at Los Angeles. Thursday-Sunday. 24 hrs. $95.

October 17-20—**10th Annual Western Regional Meeting of the Society of Nuclear Medicine** at Palm Springs. Thursday-Sunday. Contact: Justine Parker, PO Box 40279, San Francisco, CA 94140. (415) 647-0722.

October 17-20—**Quality Care in the Workers Compensation System.** USC at Los Angeles. Thursday-Sunday. 21 hrs.

(Continued on Page 416)

THE WESTERN JOURNAL OF MEDICINE

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

(Continued from Page 414)

October 18-20—**Common Office Problems for the Primary Care Physician 2nd Annual Symposium.** Monterey County Medical Society at Monterey. Friday-Sunday. 12 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

October 19—**Obesity, Brief Therapeutic Strategies for Preparing the Obese Person to Make Lasting Dietary Changes.** Mental Research Institute, 555 Middlefield Rd. at Palo Alto. Saturday. 3.5 hrs. Fee: $40. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 19-20—**Passionate Attachments: The Essential but Fragile Nature of Love.** Continuing Education Seminars at Century Plaza Hotel, Los Angeles. Saturday-Sunday. 12 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave., Los Angeles, CA 90024. (213) 475-8300.

October 21-24—**Family Crises: Intervention strategies.** Mental Research Institute at Palo Alto. Monday-Thursday. 12 hrs. Fee: $170. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 23-27—**Sexual Abuse: An Interdisciplinary Exploration.** Southern California Neuropsychiatric Institute at Ritz-Carlton, Laguna Niguel. Wednesday-Sunday. Fee: $350. Contact: Stacey W. Grace, La Jolla Blvd., La Jolla 92037. (619) 454-2102.

October 25-27—**Child Abuse.** Institute for the Advancement of Human Behavior at Anaheim. Friday-Sunday. 15 hrs. $145-$225. Contact: IAHB, 4370 Alpine Road, #205, Portola Valley, CA 94025. (415) 851-8411.

October 25-29—**The Spine: Advanced Concepts and Techniques.** The Spine Study Group at Vacation Village Hotel, San Diego. Friday-Tuesday. Contact: Spine Study Group, PO Box 13185, San Diego, CA 92103. (619) 692-9115.

October 26—**Symposium on Infectious Disease: Diagnosis and Treatment in the Office Practice.** Center for Healthcare Communications at Hilton Hotel, Sacramento. Saturday. 6 hrs. Contact: Pamela Harvey, Center for Healthcare Communications, 420 Lexington Ave., #320, New York, NY 10017. (212) 210-8940.

November 1-2—**Treating the Emotional Aspects of Cardiovascular Disease.** Monterey County Medical Society at Napa Valley. Friday-Saturday. 6 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

November 6-8—**Primary Care: Selected Current Topics.** Merritt-Peralta Health Education Center at Oakland. Wednesday-Friday. 18 hrs. Fee: $245. Contact: Merritt-Peralta, 400 Hawthorne Ave., Oakland. (415) 420-6161.

November 7-10—**Academy of Psychosomatic Medicine Annual Meeting.** Academy of Psychosomatic Medicine at San Francisco. Thursday-Sunday. Contact: Evelyne Hallberg, APM, 70 W. Hubbard St., Chicago, Ill 60610. (312) 644-2623.

November 8—**New Concepts in Medicine—21st Annual Staff Seminar.** California Medical Center at Los Angeles. Friday. 6 hrs. Fee: $35. Contact: Kenneth L. Senter, MD, Director of Medical Education, 1414 S. Hope St., Los Angeles 90015. (213) 748-4211.

November 8-9—**Update of the Treatment of Asthma.** Monterey County Medical Society at Monterey. Friday-Saturday. 6 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

November 14-16—**Clinical Preventive Medicine: 1985.** UCD at Sacramento. Thursday-Saturday. Contact: Office on Continuing Medical Education, 2701 Stockton Blvd., Sacramento 95817. (916) 453-5390.

November 16—**Systematic Aspects of Chronic Physical Pain.** Mental Research Institute at Palo Alto. Saturday. 5 hrs. Fee: $70. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

IDAHO

October 12-18—**Effective Diagnosis and Treatment of Infectious Diseases.** Salmon River, Idaho Sports Fishing. Saturday-Friday. 24 hrs. Cat I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

October 3-5—**Montana Medical Association Annual Meeting.** Outlaw Inn, Kalispell. Thursday-Saturday. Contact: NNA, 2012 11th Ave., Ste. 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 3-5—**Advanced Management of Radiation Accidents.** Albuquerque. Thursday-Saturday. AMA Cat. I. Clarion Four Seasons. Contact: UNM.

October 4-5—**Ophthalmology for Primary Care Physicians.** Albuquerque. Friday-Saturday. Marriott Hotel. 10 hrs. AMA Cat. I. Contact: UNM.

October 10-12—**New Mexico Cancer Symposium: Current Concepts in Cancer Management for Practicing Physicians.** Albuquerque. Thursday-Saturday. La Posada de Albuquerque. 13 hrs. AMA Cat. I. Contact: St Joseph Cancer Center, Albuquerque 87102. (505) 848-8000.

October 11-12—**First Balloon Fiesta Lung Disease Conference.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center Education Building. 9½ hrs. AMA Cat. I. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

October 17-19—**Primary Care Update '85: A Clinical Symposium for Physician Assistants, Nurse Practitioners and Allied Health Professionals.** Albuquerque. Thursday-Saturday. AMFAC Hotel. Contact: UNM.

November 1—**The Treatment of Coronary Artery Disease.** Albuquerque. Friday. 8 hrs. AMA Cat. I. Continental Inn. Contact: American Heart Association-New Mexico Affiliate, 629 Truman NE, Albuquerque 87108. (505) 268-3711.

November 1-2—**New Mexico Pediatric Society Annual Meeting—Infectious Diseases in Children.** Ruidoso. Friday-Saturday. Inn of the Mountain Gods. 8 hrs. AMA Cat. I. Contact: NM Pediatric Society, Marilyn Stark, Executive Secretary, 7605 Mountain Rd. NE, Albuquerque 87110. (505) 293-1333.

November 15-16—**New Mexico Medical Society Interim Meeting.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Contact: NM Medical Society, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

November 22—**Current Concepts on Causes of Cancer.** Los Alamos. Friday. Los Alamos National Labs, Meson Facility. 6 hrs. AMA and NM Cat. I. Contact: Jerry Williams, MD, PO Box 1663, MS-D421, Los Alamos 87545.

December 5-7—**New Mexico Chapter, American College of Physicians, and New Mexico Society of Internal Medicine**—Annual Meetings. Thursday-Saturday. Marriott Hotel, Albuquerque. 12 hrs. AMA Cat. I. Contact: UNM.

December 13-14—**Trauma Update '85.** Albuquerque. Friday-Saturday. Convention Center. AMA Cat. I. Contact: UNM.

February 20-22—**19th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. Hilton Inn. AMA Cat. I. Contact: UNM.

CONTACT INFORMATION

UNM—Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

EMERGENCY MEDICINE

November 14-15—**Symposium on Critical Care Medicine.** Red Lion/Jantzen Beach. Thursday-Friday. Contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 17-19—**9th Annual Pacific NW Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion/Jantzen Beach. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

October 4-5—**Fifth Annual Toxicology Conference.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

October 11-13—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

September 26-27—**Utah State Medical Association Annual Meeting.** Thursday-Friday. Hotel Utah, Salt Lake City. Contact: USMA, 540 E. Fifth South, Salt Lake City 84102. (801) 355-7477.

November 8-9—**Advanced Trauma Life Support** (Sponsor: University of Utah/Utah Department of Health). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Kim Tanner, (801) 533-6608.

January 20-23—**International Biomedical Engineering Symposium** (Sponsor: University of Utah). Monday-Thursday. Salt Lake City Salt Palace. 18 hrs. Contact: Joseph Andrade, PhD, (801) 581-7236.

April 10-12—**Neurology for the Practitioner** (Sponsor: University of Utah). Thursday-Saturday. Salt Lake City Sheraton. 18 hrs. Contact: J. Richard Baringer, MD, (801) 581-8664.

March 6-7—**Utah Ophthalmological Society Annual Park City Winter Meeting: Corneal Disease** (Sponsors: Utah Ophthalmological Society and University of Utah). Thursday-Friday. Holiday Inn/Yarrow, Park City. Contact: Pam Hanson, (801) 355-5290.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 19—**JCAH Update on Quality Assurance.** Seattle. Thursday. Marriott Hotel. Contact: Wendy Ray, Washington State Hospital Association, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

September 19-22—**Washington State Medical Association Annual Meeting.** Jantzen Beach. Thursday-Sunday. Thunderbird Motor Inn. Contact: Patti Smith, WSMA, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

(Continued on Page 423)

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NORTHERN CALIFORNIA: Physician, Board certified/eligible in Emergency Medicine or Family Practice, to work part-time or full-time in busy free-standing emergency center. Competitive compensation and malpractice paid. Send CV and references to Joanne Berkowitz, MD, The Emergency Center Medical Group, 4948 San Juan Ave., Fair Oaks, CA 95628.

IMMEDIATE OPENING—Opportunity for Internist, Cardiologist or Family Practice to join two doctor clinic grossing near $400,000. Opportunity to buy in also. Two Surgeons and over five Family Practice Doctors who will support an Internist. Central WA; (509) 422-2600.

CALIFORNIA—Board Certified/eligible or residency trained emergency physician wanted to join 320 physician multispecialty group. Competitive salary and excellent fringe benefits. Ninety miles from Sierra skiing and San Francisco. California license required. Send curriculum vitae to Mrs. Carolyn Whelan, The Permanente Medical Group, Inc., PO Box 254999, Sacramento, CA 95825. An equal opportunity employer.

CALIFORNIA, RURAL AMERICAN AND OVERSEAS: Primary care physicians and OB/GYN needed for locum and permanent placements in CA, Saudi Arabia and, southwestern US. Excellent financial package, practice management and affiliation with a dynamic healthcare company. CV to: Beverly Froley, Westworld Healthcare Resources, 23832 Rockfield Rd., Lake Forest, CA 92630; (800) 847-1596.

EMERGENCY PHYSICIAN, San Francisco Bay Area. Leading HMO seeking ABEM certified/residency trained Emergency Physician or Internist with extensive emergency medicine experience for full-time position. Competitive salary with outstanding benefits leading to shareholdership. Send CV to J. A. McCowin, MD, Emergency Dept., Permanente Medical Group, 280 W. MacArthur Blvd., Oakland, CA 94611, or call (415) 428-5634.

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URGENT CARE CLINIC: Sacramento, CA. Full time family practice oriented emergency physician. Twelve hours/day. Gurarantee plus percentage. Malpractice provided. Minimum one year commitment. For information about this position call (916) 933-1449 (evenings).

MONTANA FAMILY PRACTICE: Have the best of both worlds. BE/BC Family Practitioner needed to establish a Department of Family Practice as part of The Billings Clinic—a 62-physician multispecialty group. Enjoy practice with or without obstetrics in a regional medical center with subspecialty backup and the cultural advantages of good schools, art, drama, symphony orchestra, etc. You and your family can enjoy the wide open spaces together. There is riding, fishing, hiking, skiing, hunting, canoeing, to name a few. This is a delightful place to raise a family. Salary leading to partnership. Contact: Paul V. Hoyer, MD, The Billings Clinic, PO Box 35100, Billings, MT 59107-5100. Telephone (406) 256-2500.

GENERAL INTERNAL MEDICINE SPECIALIST position open with 35 member multispecialty group. Excellent practice opportunity, full range of benefits, immediate shareholder status, all practice costs paid. For more information contact: Colin Wells, MD, Recruitment Coordinator, or David E. Graham, Associate Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401; (805) 546-5600.

BOARD CERTIFIED OR ELIGIBLE. Family Practitioner to practice in active county outpatient clinic. Responsibilities to include shared OB, call coverage and inpatient duties. Rural northern California county with 42,000 population, four seasons and excellent local recreational opportunities. The County provides a benefit package which includes vacation, holidays and each occurrence malpractice insurance coverage. Positions may be negotiated as to individual contract or County package. Contact: Dr. Gumm, Medical Director, Tehama County Health Center, 1850 Walnut St., Red Bluff, CA 96080; (916) 527-0350.

2,000 SQUARE FEET office space available for health professional. Area in need of General Practitioner and Internist. Contact Olympic Professional Building, c/o Anita Paves, MD, 193 S. Market Blvd., Chehalis, WA 98532; (206) 748-3366.

CALIFORNIA, NORTHERN: We are seeking career-oriented emergency physicians to staff the emergency department at the new Kaiser Hospital in South Sacramento. Advantages include ideal location midway between San Francisco and the Sierra Nevada Mountains, excellent patient mix, freedom from contract billing hassles, competitive salary, and outstanding fringe benefits. Send CV to William Durston, MD, c/o Mrs. Carolyn Whelan, The Permanente Medical Group, Inc., PO Box 254999, Sacramento, CA 95825. An equal opportunity employer.

INTERNIST, Board certified/eligible to share medical suite, overhead expenses. One-year-old, thriving solo practice in Albuquerque, New Mexico's fastest growing city. Brand new spacious offices. Excellent weather, plenty of recreational opportunities. Send CV to F. Torres, MD, 4801 McMahon Blvd., N.W., Suite #250, Albuquerque, NM 87120.

FAMILY PRACTITIONER—position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus early shareholding status; excellent opportunity; central coast of California. Submit CV to Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401.

FACULTY MEMBER OF COMP looking for associate interested in structural rehabilitation. Opportunity to build an exciting practice at a large preventive medical clinic with DOs and MDs in beautiful La Jolla, California. Opening immediately. For information, contact Ruth I. Gotsch, DO, 8950 Villa La Jolla Dr., Suite 2162, La Jolla, CA 92037; (619) 457-1314.

CALIFORNIA, SONOMA COUNTY—B/C or B/E FP to associate with B/C FP in growing community 60 minutes north of San Francisco. Salary or percentage to start. Hours negotiable. Contact Thomas H. Moore, DO; (707) 795-4560.

OTOLARYNGOLOGIST with interest or fellowship in Otology (BC/BE) to join 40-physician multispecialty group in California. Well-equipped office, salary plus incentive, excellent benefits, location. Send résumé to Box 6493, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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PSYCHIATRIST—Board eligible, half-time salaried inpatient position with county/private patients. Private practice inpatient/outpatient available. Bilingual in Spanish preferred. Apply to Owen Lum, MD, Dominican Santa Cruz Hospital Mental Health Unit, 1555 Soquel Dr., Santa Cruz, CA 95060; or call (408) 476-0220, Ext. 1400.

PULMONOLOGIST, Boarded Internal Medicine and Board eligible Pulmonology, to join 35-member multispecialty group located on the California central coast. Premium location, excellent practice opportunity with fully paid benefit and retirement program; guaranteed salary first six months followed by incentive pay program; all practice costs paid. For more information contact: Colin Wells, MD, Recruitment Coordinator, or David Graham, Associate Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401; (805) 546-5600.

TWO FULL-TIME FACULTY POSITIONS available in the Department of Family Practice, University of California, Davis; level of appointment commensurate with academic experience and credentials. Should be Board certified by the American Board of Family Practice with interest, training, and/or experience in teaching, research and academic publication activities. These positions will remain open until filled . . . applications will not be accepted after 12/31/85. Send CV to Robert C. Davidson, MD, Chair, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd., Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

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(Continued on Page 422)

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(Continued from Page 420)

PHYSICIANS WANTED

PEDIATRICIAN: Immediate opening for Board eligible/certified Pediatrician with the Western Montana Clinic in an outstanding university town of 30,000 with excellent practice, recreational, and educational opportunities. Contact: Wesley W. Wilson, MD, Western Montana clinic, 515 West Front St., Missoula, MT 59802.

CALIFORNIA, SAN FRANCISCO BAY AREA: Full-time career Emergency Physician wanted for high volume Emergency Department. Emergency Medicine Board certified or Board-ready mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation; one week CME; paid malpractice, health and life insurance; corporate shareholdership in three years. Send CV or contact William Green, MD, or David Gallagher, MD, 27400 Hesperian Blvd., Hayward, CA 94545.

SEATTLE, WASHINGTON: Progressive multispeciality group, University affiliated, seeks BC/BE Family Practitioner to join developing family medicine service. Comprehensive primary care, including obstetrics. Excellent salary, benefits. Contact: Ms Y. Westover, (206) 324-5676, Pacific Medical Center, 1200 12th Ave. So., Seattle, WA 98144.

SANTA BARBARA, CA—Internist, Board certified/eligible, energetic General Internist to join well-established group of rehabilitation physicians in beautiful coastal city to provide internal medicine care for 46 bed freestanding hospital specializing in treatment of physical disabilities, e.g., strokes, spinal cord injuries, traumatic head injuries, amputees. Salary negotiable. Contact: Martin Wice, MD, Box 3098, Santa Barbara, CA 93130.

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WESTERN WASHINGTON—Private practice openings in Family Practice, Internal Medicine, Pulmonary, OB/GYN, and Otolaryngology. For information, please call Eloise Gusman, 1 (800) 535-7698; or send CV to 2800 Veterans Blvd., Suite 170, Metairie, LA 70002.

WANTED—FAMILY PRACTICE ASSOCIATE—Pleasant Central California community close to mountains, ocean, San Francisco and Los Angeles. Medical school affiliation possible. Well established general practice with light obstetrics. Salary plus incentive. Available immediately. Woman preferred. Reply to Kathleen A. Baron, MD, 1163 East Warner Ave., Fresno, CA 93710; (209) 432-1700.

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CALIFORNIA: University of California Davis Medical Center, Division of Emergency Medicine. Full-time positions are available for physicians in the Division of Emergency Medicine. We are an academic medical center and the trauma center for a large region of Northern California. The positions are clinical faculty appointments with the University of California Davis School of Medicine and entail direct patient care in the Emergency Department as well as teaching the housestaff and medical students of the University of California Davis Medical Center. Applicants should send curriculum vitae to Robert Derlet, MD, Division of Emergency Medicine, UCDMC, 2315 Stockton Blvd., Trailer 1219, Sacramento, Ca 95817.

FAMILY PRACTITIONER—Full-time position available for residency trained, Board eligible/Board certified Family Practitioners interested in practicing in a comprehensive care environment. Outpatient care and in-hospital responsibilities are offered in a growing family practice organization. Administrative responsibilities also available. For information, call William Trainor, Manager Professional Staffing, toll-free 1 (800) 446-2255; in California call 1 (800) 336-2255. FHP Professional Staffing, 400 Oceangate Blvd., Suite 1317, Long Beach, CA 90802. For opportunities in Utah, call Maryalys Poulson, collect, at (801) 355-1234.

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September 24—**Executive Survival and Effectiveness in a Changed Health Industry.** Seattle. Tuesday. Marriott Hotel. Contact: Wendy Ray, Washington State Hospital Association, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

September 28-October 4 (SAN JUAN ISLANDS)—**Effective Management of Common Sports Injuries.** Saturday-Friday. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (206) 788-4995.

October 2—**Update on Labor Laws.** Seattle. Wednesday. Red Lion Inn. Contact: Wendy Ray, Washington State Hospital Association, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

October 2-4—**ACP—Clinical Topics in Pulmonary Medicine.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

October 10-11—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. Westin. Contact: U/W.

October 17-18—**Washington State Hospital Association—Annual Meeting.** Seattle. Thursday-Friday. Red Lion Inn. Contact: Wendy Ray, WSHA, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

October 18—**Annual Cancer Conference.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 24-25—**Alzheimer's.** Seattle. Thursday-Friday. Westin. Contact: U/W.

October 25-26—**Neonatal and Pediatric Advanced Life Support.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

November 1—**Management of Common Problems in Epilepsy.** Bellevue. Friday. Red Lion Inn. Contact: Nancy Aziz, Continuing Medical Education, Overlake Hospital and Medical Center, 1035 116th Ave. NE, Bellevue 98004. (206) 454-4011, ext. 2630.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

November 1—**Frontiers in Eye Care for Health Professionals.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 1-2 (VANCOUVER)—**Northwest Urological Society 1985 Annual Meeting.** Vancouver, BC. Friday-Saturday. Bayshore Inn. Contact: Patti Smith, Northwest Urological Society, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

November 7-8—**Washington Chapter, American College of Emergency Physicians—15th Annual Clinic Conference.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington Chapter, ACEP, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

November 15—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 23-30 (HAWAII)—**Medical Malpractice: Preventive Approach.** Maui. One week. Contact: U/W.

December 6—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 7-8—**Washington State Society of Anesthesiologists Winter Meeting.** Seattle. Saturday-Sunday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

December 27-January 3 (HAWAII)—**Medical Malpractice: Preventive Approach.** Maui. One week. Contact: U/W.

January 23-24—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 7-8—**Clinical Problems in Urology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 28-March 1—**Neurology—Past, Present, Future.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

March 21-22—**Medicine for Psychotherapists.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

April 5—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 2-3—**Functional Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8-9—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC. ◆

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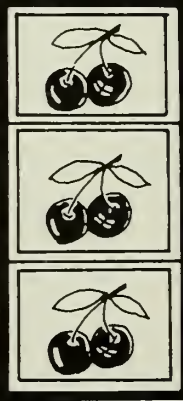

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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: June 5-7, 1986, Loews Ventana Canyon Resort, Tucson.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1986: date and place to be announced.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 2-4, 1986, Winnemucca.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Centennial Meeting: April 30-May 2, 1986, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1986: date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1986, Jackson Lake Lodge, Moran.

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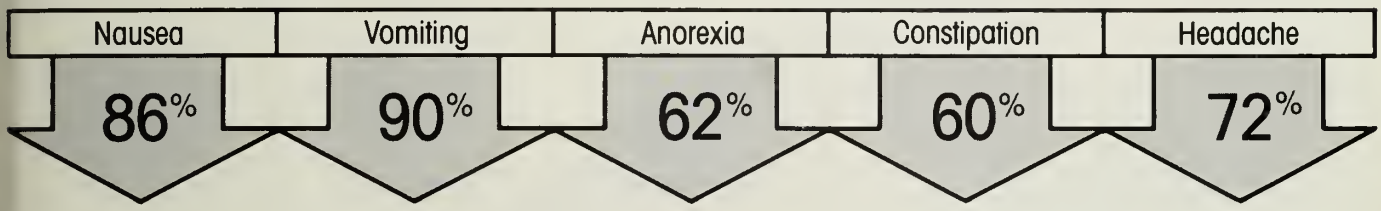

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References: **1.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ **2.** Feighner JP, *et al. Psychopharmacology 61*:217-225, Mar 22, 1979

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

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Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

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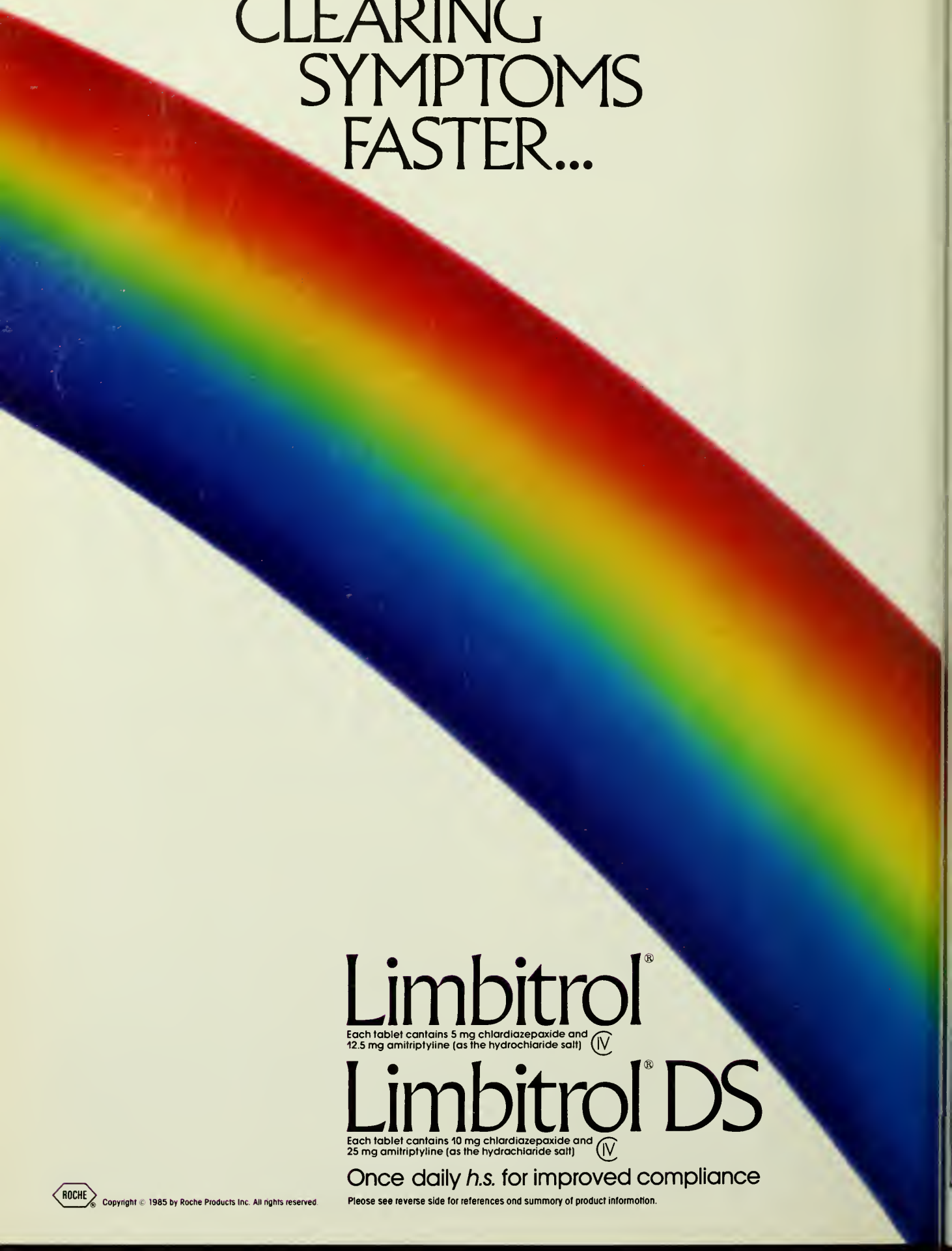

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References: **1.** Kales J, *et al: Clin Pharmacol Ther 12* 691-697, Jul-Aug 1971 **2.** Kales A, *et al. Clin Phormocol Ther 18* 356-363, Sep 1975 **3.** Kales A, *et al. Clin Phormocol Ther 19* 576-583, May 1976 **4.** Kales A, *et al: Clin Phormocol Ther 32* 781-788, Dec 1982 **5.** Frast JD Jr, DeLucchi MR: *J Am Geriotr Soc 27* 541-546, Dec 1979 **6.** Dement WC, *et al Behav Med*, pp. 25-31, Oct 1978. **7.** Kales A, Kales JD. *J Clin Psychopharmacol 3* 140-150, Apr 1983 **8.** Tennant FS, *et al:* Sympasium an the Treatment af Sleep Disarders, Telecanference, Oct 16, 1984 **9.** Greenblatt DJ, Allen MD, Shader RI *Clin Pharmocol Ther 21* 355-361, Mar 1977

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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Withdrawal symptoms rarely reported, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase, and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.
Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage, 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.
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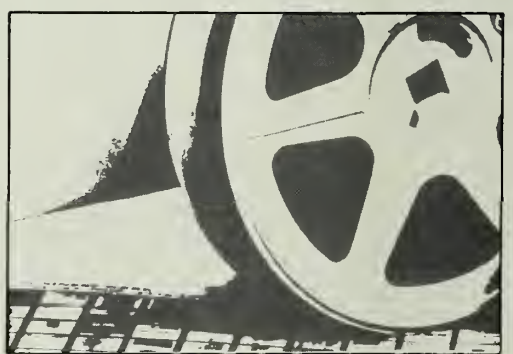

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INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg, for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg), Sustained Action Tablets (40 mg).

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‡The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

Reference:

1. Stumpe KO, Overlack A, Kolloch R, et al: Long-term efficacy of angiotensin-converting-enzyme inhibition with captopril in mild-to-moderate essential hypertension. Br J Clin Pharmacol 14(suppl 2):121S-126S, 1982.

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Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled hy conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine < 1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can he minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or hy initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may he especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic hlocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets.
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Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 18-19—**Geriatric Medicine.** Boswell Memorial Hospital, Sun City. Friday-Saturday. Contact: Western Division, American Geriatrics Society, (602) 977-1877.

October 25-26—**Therapeutic Advances: New Choices for Medical Management of Disease.** Poco Diablo Resort, Sedona. Friday-Saturday. Contact: U of A.

November 1-3—**5th Annual Southwestern Poison Symposium.** Loews Ventana Canyon Resort, Tucson. Friday-Sunday. Contact: U of A.

November 2—**Where Has Childhood Gone?** Doubletree at Scottsdale Mall, Scottsdale. Saturday. Contact: U of A.

November 9—**Cardiology.** Phoenix. Saturday. Contact: U of A.

November 15-16—**Arizona Chapter, American College of Surgeons.** Loews Ventana Canyon Resort, Tucson. Friday-Saturday. Contact: U of A.

November 16-17—**Review and Update of Gastro-intestinal Pathology.** Scottsdale Hilton, Scottsdale. Saturday-Sunday. Contact: Arizona Society of Pathologists, (602) 246-8901.

November 25-27—**Cemented Versus Uncemented Revision Total Joint Arthroplasty.** Registry Resort, Scottsdale. Monday-Wednesday. Contact: Medical Meetings Department, St. Luke's Medical Center, (602) 251-8402.

December 7—**Psychiatry.** Tucson. Saturday. Contact: U of A.

February 13-15—**Them Ol' Bones.** Scottsdale Hilton Hotel, Scottsdale. Thursday-Saturday. Contact: St. Luke's Medical Center, (602) 251-8402.

CONTACT INFORMATION

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 95724. (602) 626-6173.

February 24-26—**Emergency Care Update VIII.** University of Arizona, Tucson. Monday-Wednesday. Contact: U of A.

February 24-27—**Practical Radiology: MRI, CT, Intervention, Computers and More.** Loews Ventana Canyon Resort, Tucson. Monday-Thursday. Contact: U of A.

February 26-28—**Ninth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wednesday-Friday. Contact: Phoenix OB/GYN Society, (602) 241-1917.

February 26-March 1—**International Ophthalmic Surgery Symposium.** Loews Paradise Valley Resort, Scottsdale. Wednesday-Saturday. Contact: The Eye Foundation, (602) 257-1077.

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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

October 16-19—**Rheumatology and Clinical Immunology: An Advanced Course.** UCSF at Hotel Meridien, San Francisco. Wednesday-Saturday. 19 hrs. $225-$375.

October 25—**Current Treatment of Allergy.** PMC at San Francisco. Friday.

December 26-30—**Allergy, Drugs, and Drug Allergies.** Symposium Maui, Inc. and Hawaii Medical Association at Hawaii. Thursday-Monday. Contact: Joe Harrison, MD, Program Director Symposium Maui, PO Box 10185, Lahaina, Maui, HA. (808) 879-8182.

ANESTHESIOLOGY

October 17-26—**1985 Post ASA Annual Meeting in Hawaii.** California Society of Anesthesiologists at

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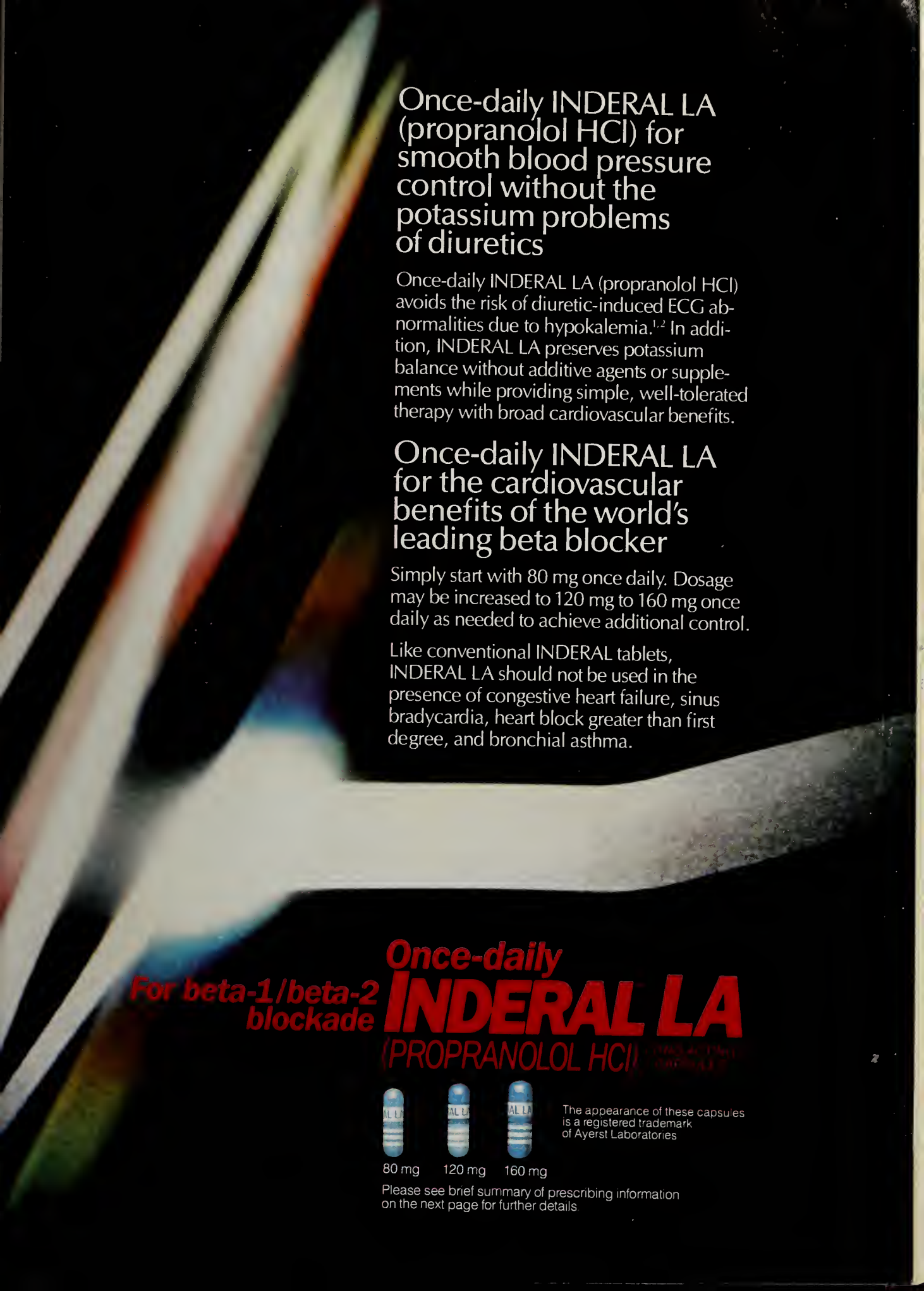

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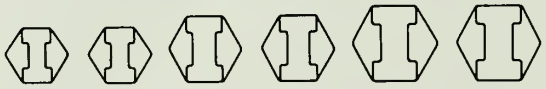

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INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

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Hotel Intercontinental, Maui, HI. Thursday-Saturday. 24 hrs. Contact: Linda P. Londerville, CSA, 100 S. Ellsworth, #806, San Mateo, CA 94401. (415) 348-1407.

November 2—**Annual Anesthesiology Symposium.** Southern California Permanente Medical Group at Westin South Coast Plaza Hotel, Costa Mesa. Saturday. Contact: Lilia M. Guerrero, Southern California Kaiser Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

CANCER

October 21-23—**9th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. 22 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 453-6222.

October 26—**Second Annual Cancer Conference.** Saint Agnes Medical Center at Fresno. Saturday. 7 hrs. Fee: $80 Physicians. Contact: Carol Withan, Cancer Program Coordinator, Saint Agnes Medical Center, 1303 E. Herndon Ave., Fresno, CA 93710. (209) 449-3570.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

November 7-8—**New Directions in Antiviral Chemotherapy.** UCSF at Holiday Inn Golden Gateway, San Francisco. Thursday-Friday.

December 11-13—**Second National Symposium on Cellular Oncology.** Memorial Medical Center of Long Beach at Palm Springs. Wednesday-Friday. 16 hrs. Contact: Assistant Director Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach, CA 90801-1428.

CARDIOLOGY

October 18-20—**Interventional Cardiology.** The Institute for Medical Studies at Las Vegas. Friday-Sunday. 15 hrs. Fee: $375. Contact: Kim Stroich, Program Coordinator (714) 495-4499.

October 18-20—**Coronary Artery Disease Hypertension, Cholesterol and Risk Factor Management.** Friday-Sunday. 16 hrs. Fee: $360 Physician. Contact: Doris Price, Educational Programs Coordinator IMEC, toll free (800) 525-8651.

October 18-20—**New Techniques and Concepts in Coronary Artery Disease Cardiology Conference.** Cedar Sinai Medical Center at Las Vegas. Friday-Sunday. 12 hrs. Contact: Lore Kahane Coordinator, Continuing Medical Education, Room 2049, PO Box 48750, Los Angeles, CA 90048. (213) 855-5547.

October 18—**Hypertension: Current Issues and Directions.** USC at Pasadena. Friday. Fee: $45. Contact: The Central Area Health Education Center. (213) 748-6152.

October 19—**Stress Emotions and the Cardiovascular System.** Cedars Sinai Medical Center at Los Angeles. Saturday. 6 hrs. Contact: Lore Kahane Coordinator, Continuing Medical Education, Cedars Sinai Medical Center Room 2049, PO Box 48750, Los Angeles, CA 90048.

October 20-27—**Cardiology for the Practitioner.** UCSF at The Ahwahnee Hotel, Yosemite. One Week. Contact: Sharon Balestra Program Representative (209) 225-6100, ext. 562.

October 24-25—**Coronary Angioplasty.** UCI at Orange. Thursday-Friday. 15 hrs. Contact: UCI CME Program Memorial Hospital Medical Center, 2801 Atlantic Ave., Box 1428, Long Beach, CA 90801. (213) 595-3837.

October 25-27—**International Symposium in the Aortic Root.** Scripps Clinic and Research Foundation at Hotel Del Coronado, San Diego. Friday-Sunday. 23 hrs. $350. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92121. (619) 453-6222.

October 25-27—**Series I Coronary Heart Disease and Arrhythmias: Diagnosis and Management.** Medical Education Resources at Las Vegas. Friday-

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ARTHUR F. GREENWALD, MD

532 **Physicians as Financial Scapegoats**
EUGENE E. BLECK, MD

532 **A Physician's Dual Responsibility in Disability—To Patients and to Society**
JOSEPH M. HUGHES, MD

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A. DAVID BARNES, MD, MPH

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ROBERT STEINBROOK, MD
From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, School of Medicine.

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ROGER A. ROSENBLATT, MD, MPH, and IRA S. MOSCOVICE, PhD
Dr Rosenblatt is Professor and Vice Chairman, Department of Family Medicine, University of Washington School of Medicine, Seattle, and Dr Moscovice is Associate Professor and Associate Director, Center for Health Services Research, University of Minnesota, Minneapolis.

541 **Computer-Assisted Assessment of Family Physicians' Knowledge About Cancer Screening Guidelines**
HOWARD D. GROVEMAN, MD; THEODORE G. GANIATS, MD; MELVILLE R. KLAUBER, PhD, and MATTHEW G. HOLDEN, MA
From the Department of Community and Family Medicine, University of California, San Diego, School of Medicine, La Jolla.

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★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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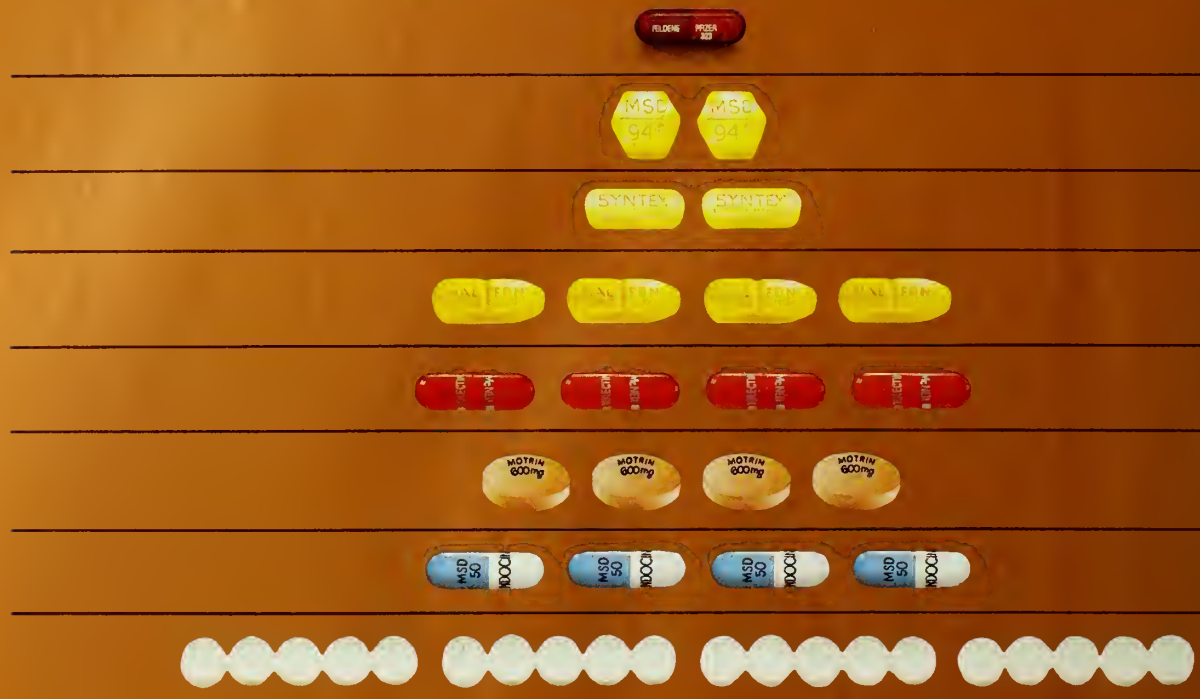

Source: PDR, 1985, Manufacturers' Prescribing Information

Indicates maximum dosage for osteoarthritis and rheumatoid arthritis for the antiarthritic agents included. Consult manufacturers' prescribing information

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice and dogs.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with FELDENE. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia.

Dermatologic: pruritus, rash.

Central Nervous System: dizziness, somnolence, vertigo.

Urogenital: BUN and creatinine elevations (see PRECAUTIONS).

Body as a Whole: headache, malaise.

Special Senses: tinnitus.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

* Reactions occurring in 3% to 9% of patients treated with FELDENE (piroxicam).

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth.

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis.

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions.

Central Nervous System: depression, insomnia, nervousness.

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS).

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS).

Special Senses: swollen eyes, blurred vision, eye irritations.

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina.

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease.

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS).

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis.

Dermatologic: onycholysis, loss of hair.

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias.

Urogenital System: dysuria.

Body as a Whole: weakness.

Cardiovascular/Respiratory: palpitations, dyspnea.

Hypersensitivity: positive ANA.

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis. It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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References: 1. Siegmeth W. Serum concentrations of piroxicam in relation to its clinical effect in patients with chronic polyarthritis. *Wien Med Wochenschr* (special issue) 31-35, 1980. 2. Tausch G. Placebo-controlled study of piroxicam in the treatment of rheumatoid arthritis. *Am J Med* (report) 72:18-22, February 1982. 3. Fogari R. Quality of life as a measure of therapeutic response. *Int Med* (special suppl) 37-43, 1984.

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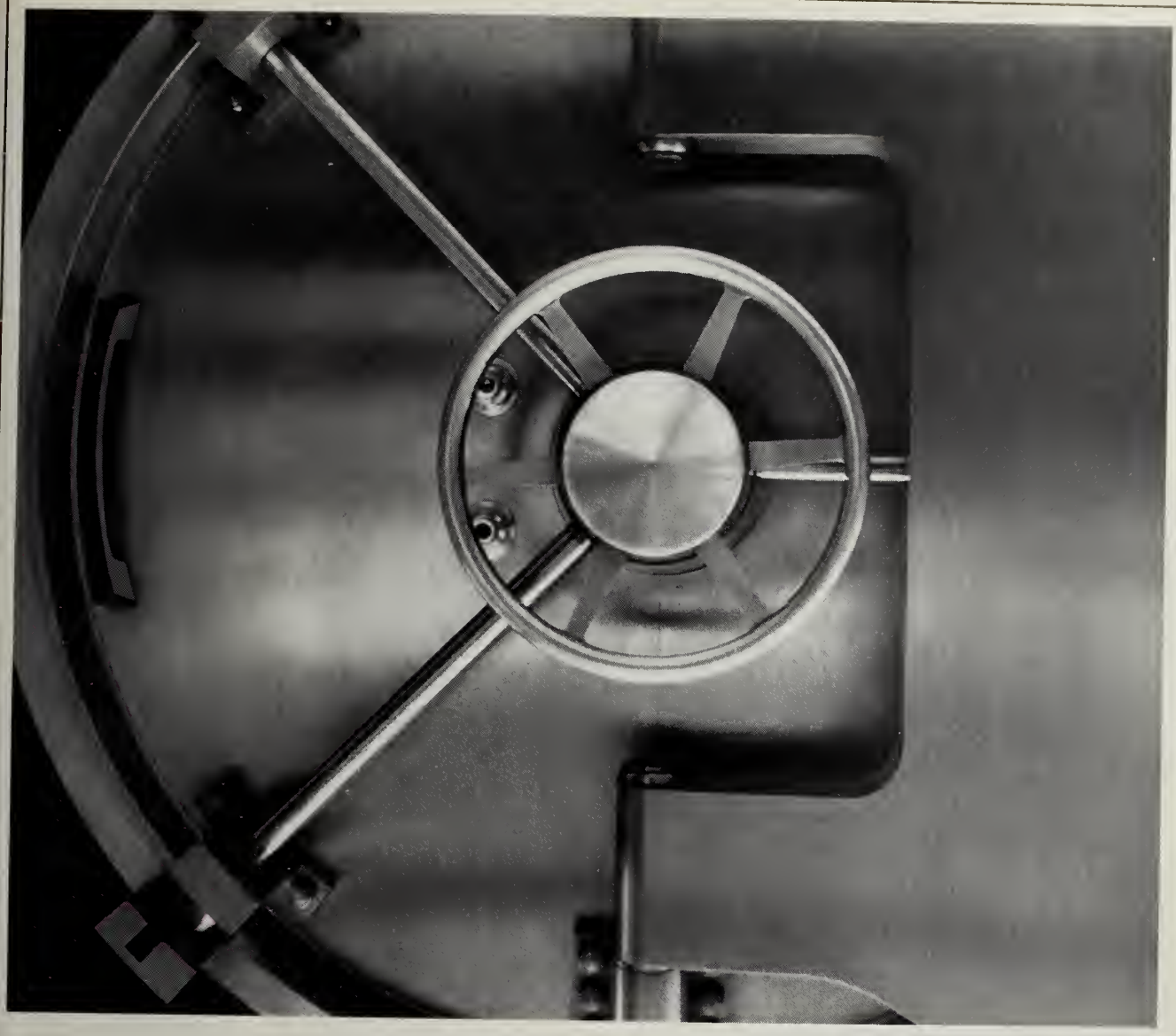

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Sunday. Contact: Leslie Shaffer, Educational Coordinator, Medical Education Resources, 5808 S. Rapp St., Ste 202, Littleton, CO 80120. 1 (800) 421-2323 or (303) 798-9682.

November 1-3—**Current Approaches to Vascular Disease.** UCSD at San Diego. Friday-Sunday. Fee: $175. Contact: Mary J. Ryals, PO Box 610203, DFW Airport, TX 75261-0203. (214) 659-9590.

December 2-6—**Chest Radiology Update and Review.** UC at San Diego. Monday-Friday. Contact: Mary J. Ryals, Ryals and Associates, PO Box 610203, DFW Airport, TX 75261-0203. (214) 659-9590.

December 4-7—**Second Annual Seminar and Workshop in Doppler Echocardiography.** UCI at San Francisco. Wednesday-Saturday. 24 hrs. Contact: Kim Stroich, The Institute for Medical Studies, 30131 Town Center Dr., Ste 215, Laguna Nuguel, CA 92677. (714) 495-4499.

December 9-10—**Antwerp-La Jolla Research Conference on Cardiac Function: Inotropic Mechanisms and Heart Failure.** UCSD. Monday-Tuesday. 13 hrs. Contact: Karen Delaney, 3960 Park Blvd., Ste F, San Diego, CA 92103 or (619) 692-9115; or PO Box 33185, San Diego, CA 92103.

December 13-15—**Advances in Heart Disease.** American College of Cardiology at San Francisco. Friday-Sunday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

EMERGENCY MEDICINE

October 16-20—**Traumatic Head Injury.** UCD at Red Lion Motor Inn, Sacramento. Wednesday-Sunday.

October 28-November 1—**Postgraduate Institute for Emergency Physicians: Symposium III.** UCSD at San Diego. Monday-Friday. 13-33 hrs. $215-$440.

October 30—**Postgraduate Institute for Emergency Physicians: Advanced Procedures Laboratory.** UCSD at San Diego. Wednesday. 3 hrs. $250.

December 1-6—**Current Concepts in Emergency Care.** Institute for Emergency Medical Education and Washington Chapter of ACEP at Hawaii. Sunday-Friday. 25 hrs. Contact: Group Travel Dept. Kailani World Travel, 4192 Meridian Ave., Bellingham, WA 98227-9951. (800) 426-2561 or WA State (800) 562-2597.

INTERNAL MEDICINE

October 12-19—**Gastroenterology: A Review.** International Conferences at Hawaii. One week. 20 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

October 16-19—**Rheumatology and Clinical Immunology: An Advanced Course.** UCSF at San Francisco, Wednesday-Sunday. 19 hrs. Fee: $225-$375.

October 17-19—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday.

October 17-20—**Practical Advances in Internal Medicine.** UCD at Napa Valley Holiday Inn. Thursday-Sunday.

October 18-20—**Practice Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** Continuing Medical Education Associates at Vacation Village, San Diego. Friday-Sunday. 20 hrs. $295. Contact: J. Shiller, CMEA, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

October 28-29—**Gynecological Histopathology.** Memorial Medical Center and UC Irvine, at Newport Beach Sheraton. Monday-Tuesday. 19 hrs. Contact: Sharon Richard, Program Coordinator Continuing Medical Education, Memorial Medical Center, Irvine.

November 4-6—**Internal Medicine.** UCSF at Yosemite. Monday-Wednesday.

November 6—**The Regulation of Glucose and Lipid Metabolism in Diabetes Mellitus: The Role of Nutrition.** American Diabetes Association Northern CA, Affiliate at Palo Alto. Wednesday. 7hrs. Fee: $55. Contact: American Diabetes Association, 1730 S. Amphlett Blvd., Room #216, San Mateo, CA 94402.

November 9—**Endocrinology.** UCSF at Fresno. Saturday. Contact: Sharon Balestra, Program Representative. Extended Programs in Medical Education. (209) 225-6100, ext. 562.

November 9-11—**Realistic Endocrinology in Primary Care.** Merritt-Peralta Health Education Center at Oakland. Saturday-Monday. Contact: Merritt-Peralta Health Education, 400 Hawthorne Ave., Oakland 94609. (415) 420-6161.

OB/GYN

October 28-November 2—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** Memorial Medical Center at Sheraton, Newport. Monday-Saturday. 42-46 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

(Continued on Page 450)

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Dr. Joyce Brothers
New York City, N.Y.

Professor Harold Ellis
Professor of Surgery, Charing Cross, Westminster Medical School, London, England.

Dr. Richard Gordon
Author of the famous "Doctor" series, London, England.

Dr. David Suzuki
Professor of Genetics, University of British Columbia, Vancouver. Science Broadcaster.

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Dr. Ejnar Eriksson • *President, International Sports Medicine Federation, Stockholm, Sweden*

Otolaryngology
Dr. D.F.N. Harrison • *U. of London, England*

Palliative Care
Dr. Balfour Mount • *Director, Palliative Care Service, Royal Victoria Hospital, Montreal*

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Dr. Paul Adams • *Prof., Child Psychiatry, U. of Texas*

Urology
Dr. Shlomo Raz • *Assoc. Prof., Surgery/Urology, U. of California, Los Angeles*

Anesthesia
Dr. Richard F.H. Catchlove • *Director, Pain Management Unit, Royal Victoria Hospital, Montreal*

Emergency Room Physicians
Dr. Robert F. Wilson • *Prof., Surgery, Wayne State U., Michigan*

Internal Medicine
Dr. Edgar Inglemann • *authority on AIDS, Assoc. Prof., Stanford University, California*

Plastic Surgery
Dr. Linton Whitaker • *Consultant Plastic & Reconstructive Surgery, Children's Hospital, Philadelphia*

National Meeting of the Occupational Medicine Assn. of Canada and the Canadian Board of Occupational Medicine
Dr. Malcolm Harrington • *Prof., Occupational Medicine, U. of Birmingham, England*

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alprazolam C-IV

THE FIRST TRIAZOLO-BENZODIAZEPINE

Its triazolo ring gives XANAX a structure uniquely different from other benzodiazepines.

THE FIRST OF A UNIQUE CLASS

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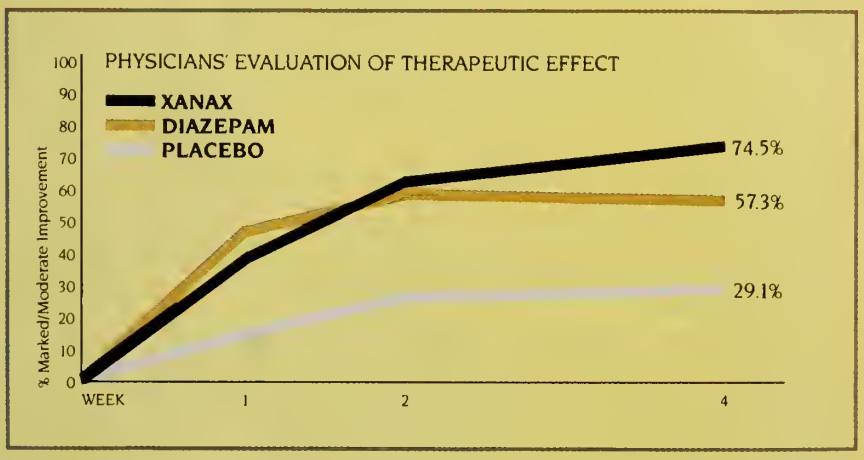
FOR CLINICAL ANXIETY

EFFICACY EQUAL TO DIAZEPAM WITH LESS DROWSINESS

In double-blind, placebo-controlled clinical trials in 976 patients with moderate to severe clinical anxiety, therapy with XANAX was compared to diazepam:*

Patients treated with XANAX *had a significantly lower incidence of drowsiness when compared directly to diazepam* therapy in *a 976-patient*, placebo-controlled, multicenter study:*

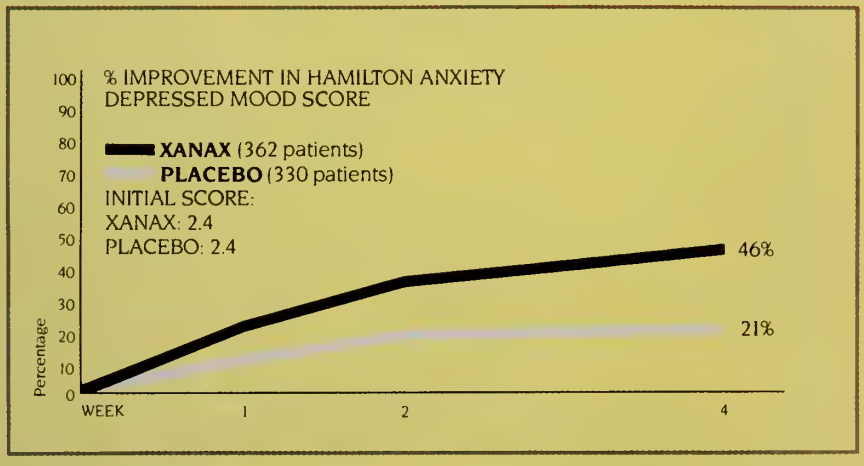


AND CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

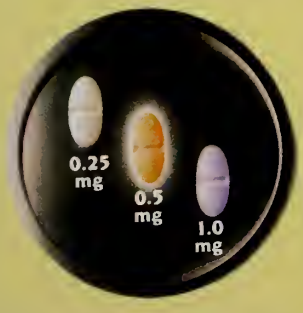
EFFECTIVE IN CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

Depressed mood is one of 14 items on the Hamilton Anxiety Rating Scale. Special analysis of 692 anxious patients with a significant depressed mood item score showed that treatment with XANAX was significantly better than placebo in decreasing depressed mood score.



SIMPLE DOSAGE:
XANAX 0.25–0.5 mg T.I.D.



The usual starting dose of XANAX is 0.25 to 0.5 mg, three times daily.

Please see next page for brief summary of prescribing information.

Xanax® 0.5 mg Tablets
alprazolam C-IV

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-3-S

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J Clin Psychiatry 42 (9):347-351, 1981.

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

J-5398 April 1985

CONTINUING MEDICAL EDUCATION

(Continued from Page 446)

October 30-November 2—**8th Annual Review Course in Clinical Obstetrics and Gynecology.** Memorial Medical Center at Irvine. Wednesday-Saturday. 7 hrs. Contact: Sharon Richard, Program Coordinator, Continuing Medical Education, Memorial Medical Center UC, Irvine.

November 11-15—**15th Annual Review of Obstetrics and Gynecology.** USC at Hilton Hotel, Pasadena. Monday-Friday. Fee: $500. Contact: USC.

November 16—**Review Course for Gynecologic Pathology.** USC at Hilton Hotel, Pasadena. Saturday. Fee: $90. Contact: USC.

December 5-8—**Current Issues in Perinatal Medicine.** Memorial Medical Center at Rancho Mirage. Thursday-Sunday. 14 hrs. Contact: Margaret Frederick, Asst. Dir. Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach, CA 90801-1428.

OPHTHALMOLOGY

November 8-10—**The Changing Eyecare Marketplace.** California Association of Ophthalmology at Palm Springs. Friday-Sunday. Contact: Barbara Lamparter, Jaech Meetings Coordinator, California Association of Ophthalmology, 2655 Van Ness Ave., #303, San Francisco, CA 94109. (415) 775-5259.

PEDIATRICS

October 25-27—**Current Advances in Pediatrics.** UC at Irvine at Disneyland Hotel, Anaheim. Friday-Sunday. 13.5 hrs. Contact: Sharon Richard, Program Coordinator, Continuing Medical Education, Memorial Medical Center, UC Irvine.

October 25-27—**Child Abuse.** Institute for the Advancement of Human Behavior at Anaheim. Friday-Sunday. Fee: $145-$225. Contact: IAHB, 4370 Alpine Rd., Ste. 205, Portola Valley, CA 94025. (415) 851-8411.

October 26-November 2—**10th Annual Pediatrics for the Practitioner.** Memorial Medical Center at Mauna Kea Beach Hotel, HI. One week. 20 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

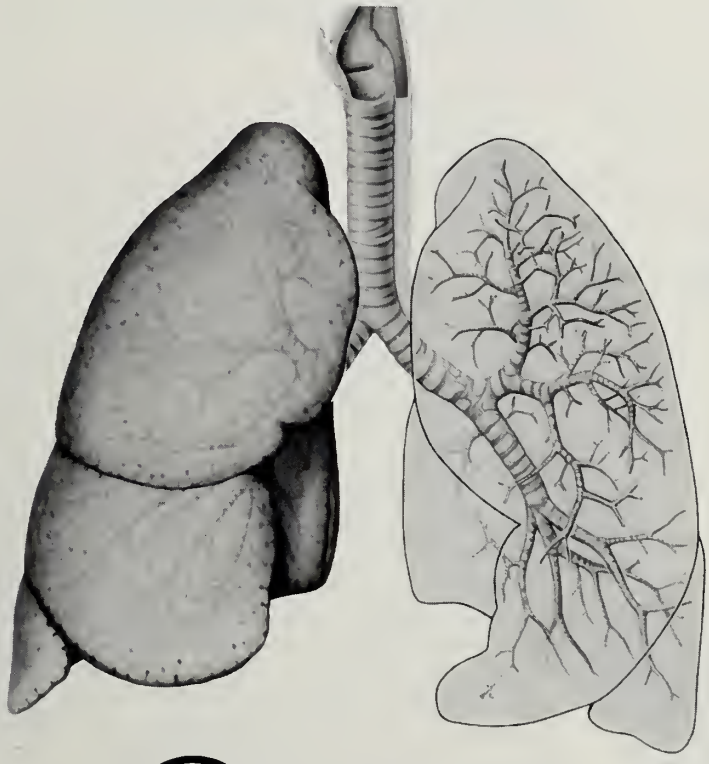
November 8-9—**Epilepsy in Childhood: Current Concepts.** UCSF at The Stanford Court, San Francisco. Friday-Saturday. Fee: $150.

November 8-9—**Child Care: The Health Providers Role.** Childrens Hospital, Oakland at Doubletree Inn, Monterey. Friday-Saturday.

November 8-11—**7th Annual Las Vegas Seminars/ Pediatric Update.** American Academy of Pediatrics

(Continued on Page 457)

Consider the causative organisms...



Ceclor®
cefaclor
250-mg Pulvules® t.i.d.

offers effectiveness against the major causes of bacterial bronchitis

H. influenzae, *H. influenzae*, *S. pneumoniae*, *S. pyogenes*
(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — Pregnancy Category B — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Lilly

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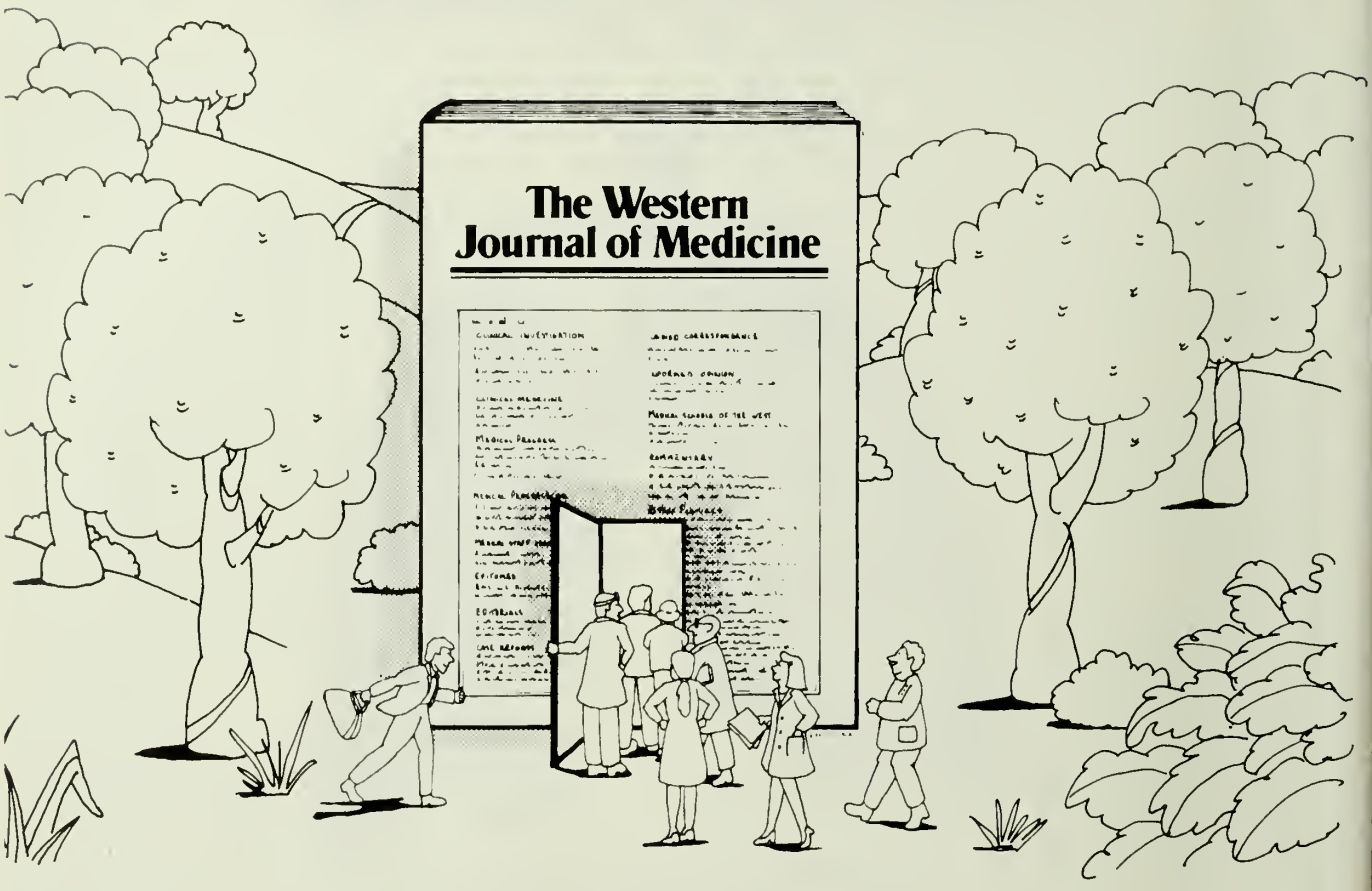
Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

Inside Information



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Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

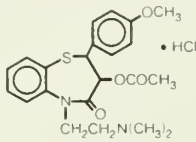
Please see full prescribing information on following page.

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm. CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina. CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LOH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted.

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LOH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LO_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LO_{50}s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NOC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NOC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NOC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NOC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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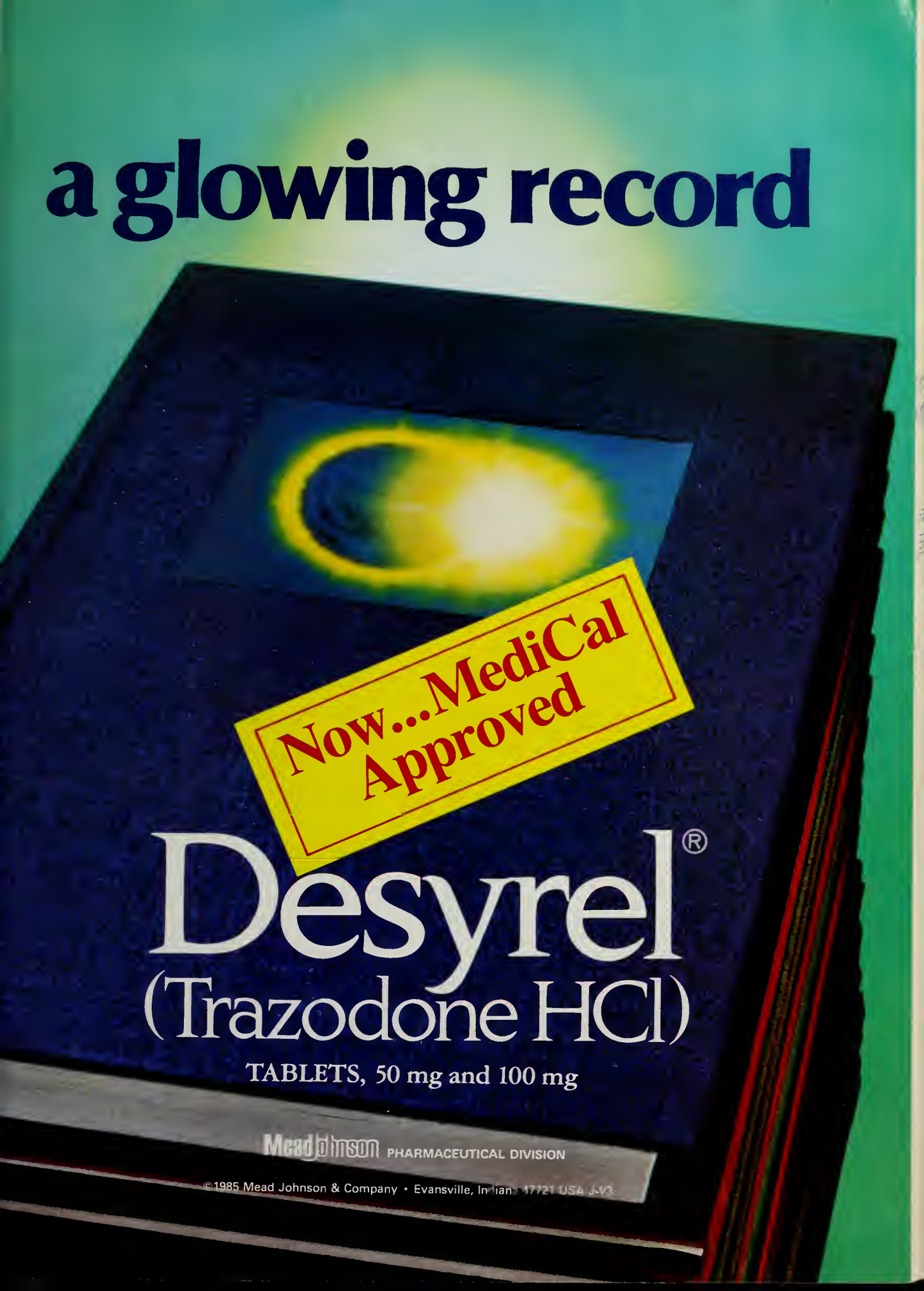
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TABLETS, 50 mg and 100 mg
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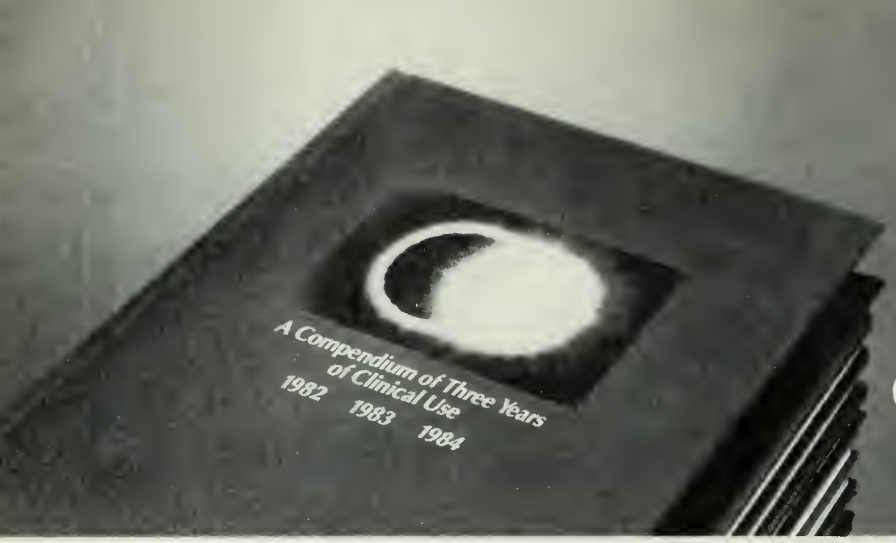

a glowing record of acceptance

Desyrel®
(trazodone HCl)

TABLETS: 50 mg, 100 mg, 150 mg

DESCRIPTION

DESYREL® (trazodone hydrochloride) is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is a triazolopyridine derivative designated as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3-(2H)-one hydrochloride. DESYREL is a white odorless crystalline powder which is freely soluble in water. Its molecular weight is 408.3. The empirical formula is $C_{19}H_{22}ClN_5O \cdot HCl$.

INDICATIONS AND USAGE

DESYREL® (trazodone hydrochloride) is indicated for the treatment of depression. The efficacy of DESYREL has been demonstrated in both inpatient and outpatient settings and for depressed patients with and without prominent anxiety. The depressive illness of patients studied corresponds to the Major Depressive Episode criteria of the American Psychiatric Association's Diagnostic and Statistical Manual, III.[a]

CONTRAINDICATIONS

DESYREL is contraindicated in patients hypersensitive to DESYREL.

WARNINGS

TRAZODONE HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN APPROXIMATELY 1/3 OF THE CASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A PORTION OF THESE CASES, PERMANENT IMPAIRMENT OF ERECTILE FUNCTION OR IMPOTENCE RESULTED. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS SHOULD IMMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

Recent clinical studies in patients with pre-existing cardiac disease indicate that DESYREL may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, and in two patients short episodes (3-4 beats) of ventricular tachycardia. Until the results of prospective studies are available, patients with pre-existing cardiac disease should be closely monitored particularly for cardiac arrhythmias. There have also been post-introduction reports of arrhythmias in DESYREL-treated patients, some of whom did not have pre-existing cardiac disease. DESYREL is not recommended for use during the initial recovery phase of myocardial infarction.

PRECAUTIONS

General: The possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Therefore, prescriptions should be written for the smallest number of tablets consistent with good patient management. Hypotension, including orthostatic hypotension and syncope, has been reported to occur in patients receiving DESYREL. Concomitant administration of antihypertensive therapy with DESYREL may require a reduction in the dose of the antihypertensive drug. Little is known about the interaction between DESYREL and general anesthetics, therefore, prior to elective surgery, DESYREL should be discontinued for as long as clinically feasible. As with all antidepressants, the use of DESYREL should be based on the consideration of the physician that the expected benefits of therapy outweigh potential risk factors. **Information for Patients**: Alert patients that (a) because priapism has been reported to occur in patients receiving DESYREL, patients with prolonged or inappropriate penile erection should immediately discontinue the drug and consult with the physician, (b) their mental or physical ability to perform potentially hazardous tasks, such as operating machinery or driving, may be impaired, (c) the response to CNS depressants such as alcohol or barbiturates may be enhanced, and (d) DESYREL should be taken shortly after a meal or light snack. **Laboratory Tests**: WBC and differential counts are recommended for patients who develop fever, sore throat or other signs of infection. Discontinue DESYREL if WBC or absolute neutrophil count falls below normal. **Drug Interactions**: Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving DESYREL (trazodone hydrochloride) concurrently with either of those two drugs. Since it is not known whether an interaction will occur between DESYREL and MAO inhibitors, therapy should be initiated cautiously with a gradual increase in dosage until optimum response is achieved, if a MAO inhibitor is discontinued shortly before or is to be given concomitantly with DESYREL. **Therapeutic Interactions**: Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving DESYREL in daily oral doses up to 300 mg/kg for 18 months. **Pregnancy**: Since there are no adequate and well-controlled studies in pregnant women, DESYREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers**: Since DESYREL and/or its metabolites have been found in the milk of lactating rats, caution should be exercised when DESYREL is administered to a nursing woman. **Pediatric Use**: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Clinical Trial Reports: Side effects reported by more than 1% of the patients during clinical trials are the following. **Autonomic**—blurred vision, constipation, dry mouth. **Cardiovascular**—hypertension, hypotension, shortness of breath, syncope, tachycardia/palpitations. **CNS**—anger/hostility, confusion, decreased concentration, disorientation, dizziness/light-headedness, drowsiness, excitement, fatigue, headache, insomnia, impaired memory, nervousness. **Gastrointestinal**—abdominal/gastric distress, bad taste in mouth, diarrhea, nausea/vomiting. **Musculoskeletal**—musculoskeletal aches/pains. **Neurological**—incoordination, paresthesia, tremors. **Sexual Function**—decreased libido. **Skin**—allergic condition/edema. and **Other**—decreased appetite, eyes red/tired itching, head full-heavy, malaise, nasal/sinus congestion, nightmares/vivid dreams, sweating/clamminess, tinnitus, weight gain, weight loss. Side effects reported by less than 1% of the study patients are the following: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusions, hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, and retrograde ejaculation. **Post Introduction Reports**: Voluntary reports received since market introduction include the following: agitation, apnea, diplopia, edema, grand mal seizures, hallucinations, hemolytic anemia, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequently), paresthesia, priapism (see PRECAUTIONS, Information for Patients, some patients have required surgical intervention), rash, ar weakness. Cardiovascular system effects which have been reported are the following: orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including ventricular tachycardia (see WARNINGS).

OVERDOSE

Signs and Symptoms: Death from overdose has occurred in patients ingesting DESYREL (trazodone hydrochloride) and other drugs concurrently (namely, alcohol, alcohol + chloral hydrate + diazepam, amobarbital, chlordiazepoxide, or meprobamate). The most severe reactions reported to have occurred with overdose DESYREL alone have been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. DESYREL should be taken shortly after a meal or light snack. **Usual Adult Dosage**: An initial dose of 150 mg/day in divided doses is suggested. Th dose may be increased by 50 mg/day every three to four days. The maximum dose fo outpatients usually should not exceed 400 mg/day in divided doses. Inpatients may given up to but not in excess of 600 mg/day in divided doses. **Maintenance**: Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Once an adequate response has been achieved, dosage may b gradually reduced, with subsequent adjustment depending on therapeutic response.

HOW SUPPLIED

DESYREL® (trazodone hydrochloride) 50 mg and 100 mg scored tablets, and 150 mg DIVIDOSE® tablets.

CAUTION: Federal law prohibits dispensing without a prescription.

REFERENCES

a. Williams JBW, Ed. Diagnostic and statistical manual of mental disorders-III, American Psychiatric Association, May 1980.

US Pat. No. 4,215,104 Date of Latest Revision: July 1

Mead Johnson

PHARMACEUTICAL DIVISION

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(Continued from Page 450)

at Inglewood. Friday-Monday. Fee: $250. Contact: American Academy of Pediatrics, Chapter 2, PO Box 2134, Inglewood 90305.

November 22-25—**Clinical Pediatrics.** American Academy of Pediatrics at Las Vegas. Friday-Monday. Contact: Eve Black, Exec. Sec., PO Box 2134, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

October 18-20—**Mind of a Murder.** Southern California Psychiatric Society at Hotel Del Coronado, San Diego. Friday-Sunday. 9 hrs. $95. Contact: Sharon Karp, 2001 S. Barrington Ave., #214, Los Angeles, CA 90025. (213) 477-1041.

October 25-27—**9th American Imagry Conference.** International Imagry Association at Ambassador Hotel, Los Angeles. Friday-Sunday. Fee: $120, $140 after October 18. Contact: International Imagry Association, PO Box 1046, Bronx, New York 10471 (Judy Marks).

November 2—**Structural Family Therapy Beyond the Basics.** Mental Research Institute at Palo Alto. Saturday. 6 hrs. Fee: $75. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 4-8—**Couple and Family Therapy Conflict and Change.** Mental Research Institute at Palo Alto. Monday-Friday. 15 hrs. Fee: $180. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 9—**Structural and Strategic Family Therapies: A Dialogue.** Mental Research Institute at Palo Alto. Saturday. 6 hrs. Fee: $75. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. 321-3055.

November 22-24—**Guided Imagery for Clinicians.** Institute for the Advancement of Human Behavior at Honolulu, Hawaii. Friday-Sunday. Fee: $245-$350. Contact: IAHB, 4370 Alpine Rd., Ste. 205, Portola Valley 94025. (415) 851-8411.

RADIOLOGY

October 19-20—**Head and Neck Radiology: Advanced Techniques in Diagnostic Imaging.** UCSF at Hyatt Regency, San Francisco. Saturday-Sunday. 12 hrs. $175-$275.

October 19-20—**Magnetic Resonance Imaging for Technologists.** UCSF at Hyatt Regency, San Francisco. Saturday-Sunday.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency, San Francisco. Monday-Friday. 31 hrs. $375-$475.

(Continued on Page 460)

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The University of Texas
Southwestern Medical School at Dallas

John M. Luce, MD
Assistant Professor of Medicine and Anesthesia
University of California, School of Medicine
San Francisco, California

Lawrence Marshall, MD
Professor and Chief Neurosurgical Services
University of California, School of Medicine
San Diego, California

Ian G. Walker, MD
Former Assistant Professor of Plastic Surgery
University of Texas, Medical Branch
Galveston, Texas
Director, Burn Unit, Penrose Hospital

Walter R. Wilson, MD
Internal Medicine—Infectious Disease
Rochester, Minnesota

For further information contact Jan Hodge-VonDeBur at (303) 475-5675 or write: Continuing Medical Education, 1400 E. Boulder, P.O. Box 1326, Colorado Springs, CO 80901.

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Motrin® Tablets
(ibuprofen)
Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis. Relief of mild to moderate pain and primary dysmenorrhea. Safety and efficacy in children are not established.
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with MOTRIN.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.
MOTRIN can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, blurred vision, skin rash, weight gain, or edema. Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when MOTRIN is added.
The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (eg, eosinophilia, rash, etc.), MOTRIN should be discontinued.
In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.
Drug interactions—*Aspirin:* used concomitantly may decrease MOTRIN blood levels.
Coumarin: bleeding has been reported in patients taking MOTRIN and coumarin.
Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal, of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.
Incidence Greater Than 1% (but less than 3%)—Probable Causal Relationship
Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).
Incidence Less Than 1%—Probable Causal Relationship*
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence Less Than 1%—Causal Relationship Unknown*
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis, cataracts; **Hematologic:** Bleeding episodes (eg, epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction, acidosis; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema; **Renal:** Renal papillary necrosis.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Do not exceed 3200 mg/day.
Rheumatoid arthritis and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
How Supplied:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
Bottles of 500	Bottles of 500	Bottles of 100
Unit-dose package of 100	Unit-dose package of 100	Bottles of 500
Unit of Use bottles of 100	Unit of Use bottles of 100	

Caution: Federal law prohibits dispensing without prescription. *For additional product information, see your Upjohn representative or consult the package insert.*
*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
Upjohn The Upjohn Company, Kalamazoo, Michigan 49001 USA
MED B-8-S
June 1985
J-5503

CONTINUING MEDICAL EDUCATION

(Continued from Page 457)

October 28-November 1—**10th Annual San Diego Postgraduate Radiology Course.** UCSD at San Diego. Monday-Friday. $425. Contact: Mary J. Ryals, PO Box 610103, Dallas Fort Worth Airport, TX 75261. (214) 659-9590.

November 4-8—**Diagnostic Radiology Seminars.** UCSF at Maui Marriott Resort, Hawaii. Monday-Friday. Fee: $375-$475. Contact: UCSF.

SPORTS MEDICINE

October 24-25—**Sports Medicine Hawaii: International Endurance, Sports and Fitness Symposium II.** UCI at Sheraton Royal Waikoloa, Kona, HI. Thursday-Friday. 16 hrs. $90-$240. Contact: J. Massimino, MD, 896 Town and Country Office Park, Orange, CA 92668. (714) 989-3432.

November 1-3—**Sports Medicine and Outpatient Orthopedics for the Primary Care Physician.** Continuing Medical Education Association at Hotel Intercontinental San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

November 1-6—**Women's Sports Medicine Update.** UCD at Hyatt Regency, Monterey. Friday-Wednesday. Contact: Office of Continuing Medical Education, School of Medicine, UC Davis, 2701 Stockton Blvd., Sacramento 95817. (916) 453-5390.

SURGERY

October 19-20—**Anterior Cruciate Ligament.** Memorial Medical Center at Long Beach. Saturday-Sunday. 10.5 hrs. Contact: Margaret Frederick, Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428. (213) 595-3811.

October 19-26—**7th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott Hotel, Hawaii. One week. 36 hrs. $875.

November 1-4—**Cyriax Approach to Orthopaedic Medicine.** Thomas A. Dorman, MD, at San Luis Obispo. Friday-Monday. 24 hrs. Fee: $420. Contact: Thomas A. Dorman, MD, 1041 Murray Ave., San Luis Obispo 93401. (805) 544-3126.

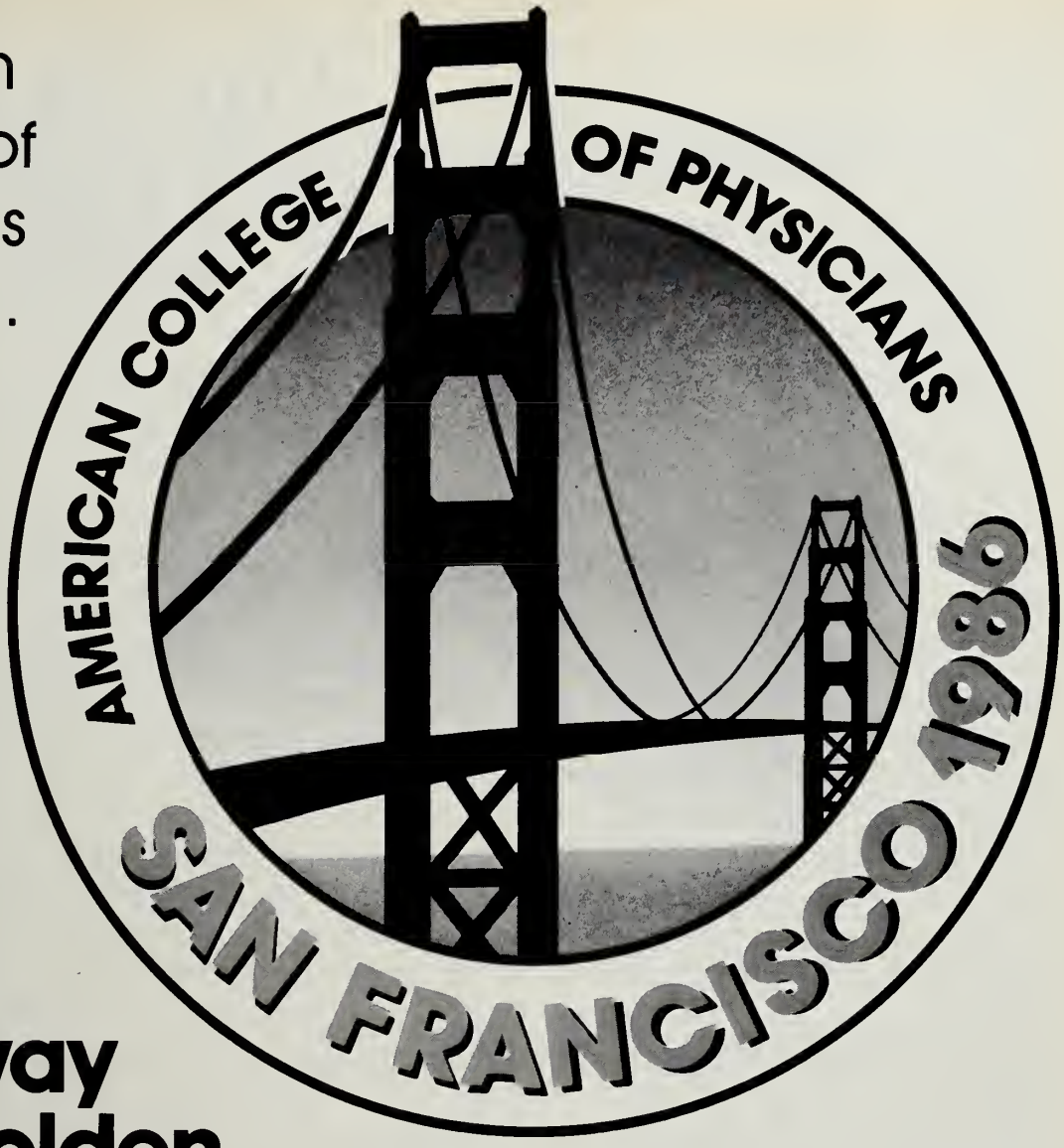
November 2—**Spinal Cord Injury Update.** UCD at Sacramento. Saturday. Contact: Office of Continuing Medical Education, School of Medicine, 2701 Stockton Blvd., Sacramento 95817. (916) 453-5390.

November 16—**Lasers on Clinical Medicine and Surgery.** Memorial Medical Center at Long Beach. Saturday. 7 hrs. Contact: Assistant Director Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach, CA 90801-1428.

December 7-8—**Lasers for Facial Aesthetics.** American Academy of Facial Plastic and Reconstructive

(Continued on Page 553)

American College of Physicians presents...



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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

★ **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: **'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

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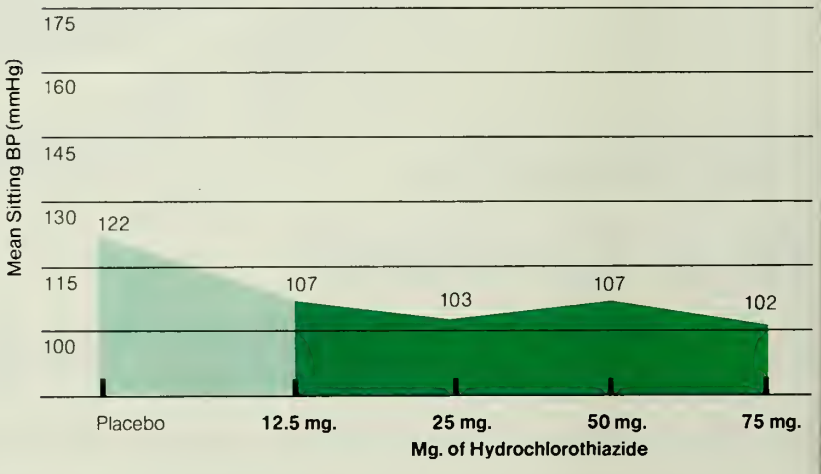

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1 Kaplan, N Systemic Hypertension: Therapy, in Braunwald, E. (ed.), Heart Disease. A Textbook of Cardiovascular Medicine, Philadelphia, W B Saunders Co., vol 1, pp. 922-951

2 Dialogues in Hypertension, Hypertension Update II· New Developments in Antihypertensive Therapy, Jan 1985, Health Learning Systems Inc.

3 Adapted from Beerman, B., and Groschinsky-Grind, M.: Antihypertensive Effect of Various Do· of Hydrochlorothiazide and Its Relation to the Plasma Level of the Drug, Eur. J. Clin. Pharmacol. 13: 195-201, 1978

Clinical Investigation

A New Method for Assessing Right-Sided Heart Pressures Using Encapsulated Microbubbles—A Preliminary Report

STEPHEN OESTERLE, MD; THOMAS SAHINES; CHARLES TUCKER, MD; E. GLENN TICKNER; JULIA RASOR; ROBERT KERNOFF; NIKI KANTROWITZ, MD; MARGARET BILLINGHAM, MD; LEE WAGNER, MD, *and* RICHARD L. POPP, MD, *Stanford, California*

A new noncatheter method for measuring pressures of the right side of the heart uses specially manufactured microbubbles of carbon dioxide injected into the peripheral venous system. Sudden expansion of these bubbles in the cardiac chambers causes bubble oscillations at a frequency that is primarily a function of surrounding pressure. The oscillations are recordable by a microphone on the chest wall. The preliminary experience has been in dogs and further development is needed before we can begin clinical testing of the method. In its current form, the potential for measuring higher systolic pressures seems better than that for lower diastolic pressures.

(Oesterle S, Sahines T, Tucker C, et al: A new method for assessing right-sided heart pressures using encapsulated microbubbles—A preliminary report [Clinical Investigation]. West J Med 1985 Oct; 143:463-468)

Documentation of pulmonary hypertension currently requires catheterization of the right side of the heart. This diagnosis can be suggested by physical examination, chest roentgenography, electrocardiography, Doppler and standard echocardiography, but quantitative confirmation is still most often obtained invasively. The clinical suspicion of pulmonary hypertension (either primary or secondary) arises so commonly that a noninvasive method of quantitating right-sided heart pressures is desirable.

A new, minimally invasive method has been tested previously in vitro[1] and recently tested in vivo in our laboratory. The early results are presented herein. Initial studies in dogs were progressively modified, so data from all available experiments are not directly comparable. But we report this preliminary assessment of a new technology for determining pressures of the right side of the heart mainly to show the principles and methods involved.

Theory

Bubbles behave as simple reflectors and oscillators under certain conditions and theoretically they can be used to measure pressure within the body noninvasively. Because bubbles are resonant scatterers of ultrasound while normal structures within the body, such as erythrocytes and tissue, are not, oscillatory signals from bubbles can be identified. Horton and Wells recognized this and developed an ultrasonic echo-ranging reflection device to detect the existence of microbubbles within the body for management of dysbarism ("the bends").[2] Fairbank and Scully proposed a transmission, absorption method to detect resonating bubbles within the heart that could provide a measure of cardiac pressure.[3] Shortly thereafter, Tickner and Rasor proposed two methods whereby the dynamics of bubbles could be used to measure pressure.[4]

The method used in our studies involved injecting pressurized microbubbles that were spontaneously released within the heart to oscillate by expanding and contracting.[4] This was accomplished by placing the pressurized carbon dioxide microbubble within a fused saccharide particle. These particles begin to dissolve following mixing with blood and, at a critical point, they fracture, releasing the bubble into the circulation. The sudden expansion causes the bubble to oscillate, or "ring," at its natural frequency of compressional oscillation. The oscillation decays in roughly 10 to 12 full cycles. These

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Submitted, revised, April 12, 1985.
Reprint requests to Richard L. Popp, MD, Cardiology Division, Department of Medicine, Stanford University Medical Center, Stanford, CA 94305.

brief oscillation signals can be detected and the frequency data transformed to determine intracardiac pressures (Figure 1).[1]

The ringing frequency of a bubble is given as follows[5-7]:

$$f = 1/\pi d\,(3\gamma p/\rho)^{1/2} \quad (1)$$

where f is the oscillatory frequency of the bubble, d is the diameter of the bubble, p is the absolute pressure of the gas in the bubble, γ is the specific heat ratio of the gas and ρ is the density of the liquid. If the physical properties and bubble diameter are known, then the bubble oscillatory frequency uniquely indicates the surrounding pressure.

Because the diameter of the gas bubble depends on its volume (V) ($d = [6V/\pi]^{1/3}$) and the pressure and volume are related by the compressibility equation (PV^n = constant), equation 1 reduces to

$$P = P_0(f/f_0)^c \quad (2)$$

where the subscript zero refers to the reference condition—that is, atmospheric pressure—and c is a constant depending on the gas. Taking logarithms and differentiating equation 2 yields

$$\Delta P/P_0 = c\Delta f/f_0 \quad (3)$$

Equation 3 indicates that changes in pressure can be directly determined by changes in the resonant frequency of bubbles in the pressure system. *Uniform* microbubbles all "ring" at the same frequency and will show a shift in ringing frequency by a given amount when pressure is changed. In this work the microbubble material was formed at 102 microns diameter and 1 atm pressure.

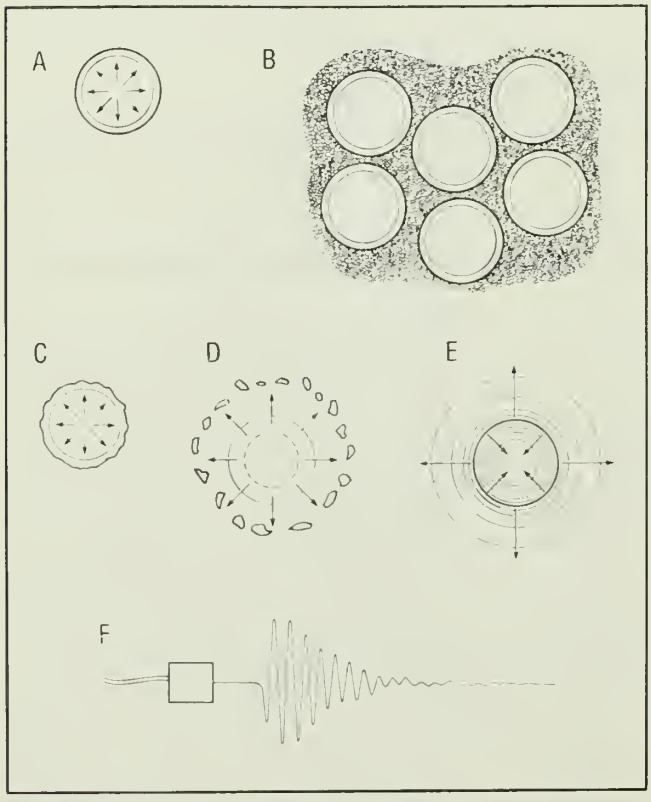

Figure 1.—Schematic representation of the origin of the signals recorded for conversion to pressure measurement. **A,** Carbon dioxide is used to form a bubble, which is incorporated into a fused saccharide particle at greater than atmospheric pressure. The particles and bubbles are uniform in size. **B,** Several thousand particles are suspended in a nonaqueous vehicle for intravenous injection. **C,** The saccharide shell begins dissolving in serum as the particles disperse in the cardiac chambers. **D,** The thinning saccharide shell fractures, releasing the pressurized gas. **E,** The gas bubble expands to a size related to the surrounding intracardiac pressure and briefly oscillates. **F,** The oscillatory signals are of ultrasonic frequency but can be recorded by an appropriate microphone.

Release of these uniform bubbles from their saccharide coat depends both on their separation from the carrying vehicle and the time necessary to fracture their capsules. Because the release of all bubbles is not simultaneous, signals occur continuously throughout the cardiac cycle and a precise signal-time record can be obtained. These data can be transformed to a pressure-time plot spanning the cardiac cycle. Electrocardiographic (ECG) gating allows signals from various periods in the cardiac cycle to be analyzed; hence, diastolic and systolic pressures can be determined.

The accuracy of this method of detecting free-ringing signals and converting them into pressure depends on uniformity of the bubble size, as mentioned. Aside from nonuniformity of bubbles, signal error can occur when bubbles are not released as perfect spheres. These deformational oscillations create frequency characteristics quite different from the uniform frequency emitted through compressional oscillation of spherical bubbles. Reflections and transducer artifacts are additional sources of error. Artifactual signals, deformational oscillation and coincident signals may be identified by their form and electronically eliminated.

Figure 2 presents a schematic of the electronic package required to transform the free-ringing oscillatory signals into pressure data. The individual components of this package and their functions are as follows:

Ultrasonic Detector (Microphone Transducer)

Signals from the oscillating bubbles are compression waves with ultrasonic frequencies of about 40 kHz. Sound signals in this range are transmitted through body tissues with little attenuation.[8] An ultrasonic microphone properly positioned on the chest wall can detect the signals coming from within the heart.

ECG Electrodes

An electrocardiographic recording is necessary to "gate" data acquisition during various intervals in the cardiac cycle. This gating technique organizes the data so signals during a given interval of time, such as systole, can be separated from other periods of the cardiac cycle. This results in grouping the pressure data into bins or ranges related to time intervals during the cardiac cycle.

Signal Conditioners

Signal conditioners serve to amplify both the oscillation and ECG signals while filtering extraneous high- and low-frequency noise. Some extraneous signals are excluded by this stage, such as deformational oscillation of nonspherical bubbles.

Microprocessor

The microprocessor decodes oscillation signals and time relative to the electrocardiographic QRS signal and subsequently converts these data into pressure-time pairs. The microprocessor also handles the statistics for the large number of sampled data.

Graphics Terminal

The graphics terminal displays oscillation frequency-time and pressure-time plots. Figure 3 shows a hypothetical idealized plot of frequency of oscillation versus time and a hypothetical plot of derived pressures versus time for the right side of the heart. This figure is included only to show the conceptual possibilities of the apparatus in the future.

Methods

Several protocols were used in ten animals while developing a useful model for evaluating the optimal microbubble expansion technique material and a suitable vehicle. The following is a description of our final working model.

Healthy 25-kg (55-lb) mongrel dogs were premedicated with morphine sulfate (2 mg per kg of body weight) intramuscularly, then anesthetized with chloralose (85 mg per kg) and urethane (625 mg per kg) given intravenously. A cuffed endotracheal tube was inserted and the animals were ventilated with room air using a Harvard respirator. Arterial blood specimens were analyzed frequently using a Corning blood gas analyzer (Model 165), and tidal volume and respiratory rate were adjusted to maintain the level of arterial oxygen pressure above 80 mm of mercury and the pH between 7.35 and 7.45. The dogs were placed on a heating pad in the supine position and four limb leads were attached for ECG monitoring. A fluid-filled catheter was placed in the descending aorta by way of the left femoral artery. A second fluid-filled catheter was placed in the superior vena cava by way of the right internal jugular vein, and a small catheter was inserted percutaneously into the left cephalic vein to be used as a conduit for infusing fluids and drugs. The chest was opened using a midline sternotomy and the heart was exposed in a pericardial cradle. A solid-state pressure transducer (Biotec, BT-250) was placed through a stab wound into the right ventricular outflow tract. A thermocouple was placed in the left ventricular apex through a stab wound to monitor blood temperature using a YSI-telethermometer.

Hemodynamic recordings were made using a multichannel electrostatic recorder (Gould ES 1000). Aortic pressures were recorded using a Statham P23Db transducer. The zero level for all pressure measurements was estimated at the mid-chest.

Compressional oscillation signals were detected over the right ventricle using an ultrasonic microphone (Bruel and Kjaer hydrophone Model #8103) and recorded on a Tektronix (Model #7603) oscilloscope. Simultaneous pressure, ECG and oscillation frequency data were recorded on high-fidelity frequency-modulation magnetic tape. Paired hemodynamic and gated frequency data were subsequently analyzed using a microprocessor (Hewlett-Packard 9826 desk-top calculator). Plots were made of the measured right ventricular pressure (solid-state transducer) versus signal frequency or signal-derived pressure (or both). Signal frequency points on these plots represent the average from more than 100 bubbles sampled.

Precision microbubble material* consisted of pressurized (1 atm) carbon dioxide bubbles (102 microns) in a fused saccharide capsule (external diameter = 144 microns) (Figure 4). The carrying vehicle was a polyalcohol.

Following instrumentation of the dog, multiple short injections of the microbubble material were delivered while varying the right ventricular pressure. Increases in right ventricular pressure were initially achieved pharmacologically by peripheral infusions of prostaglandin F_{2a} (Upjohn Company, Kalamazoo, Michigan), which produces pulmonary hypertension.[9,10] Right ventricular pressures were also raised abruptly by partial mechanical obstruction of the pulmonary artery with finger pressure. The microbubble material was

*Supplied by Rasor Associates, Sunnyvale, California.

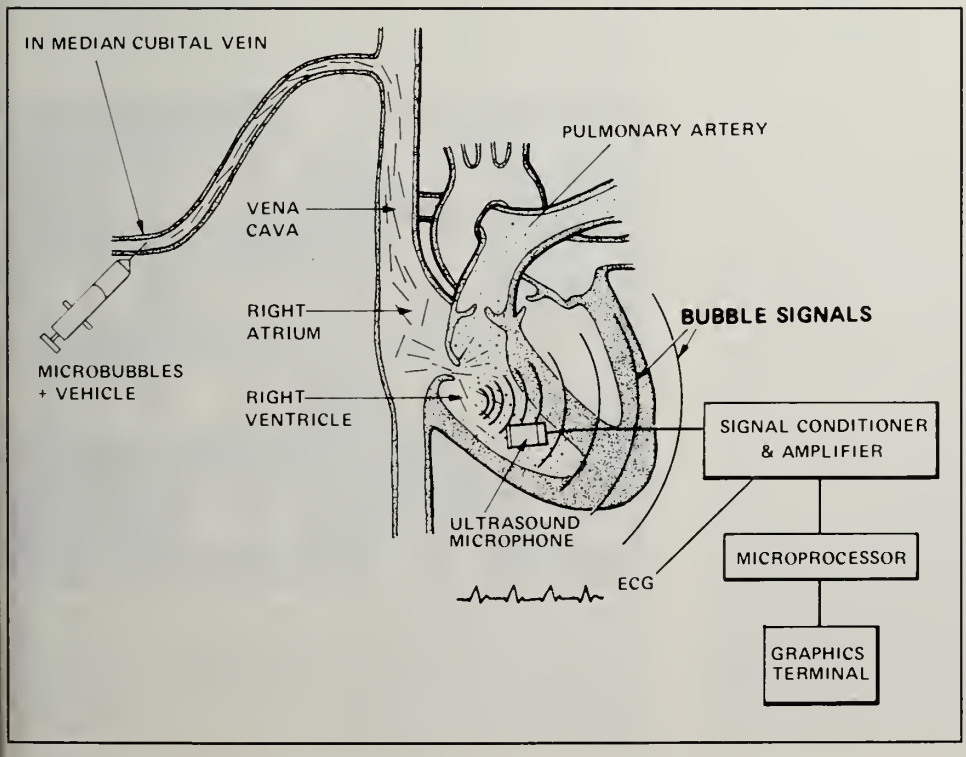

Figure 2.—Schematic representation of the electronic package required to transform the free-ringing oscillatory signals into pressure data. See text for full explanation. ECG = electrocardiogram

TABLE 1.—*Raw Data Relating Catheter-Measured Pressure to Pressure Calculated From Microbubble Frequency Data*

Pressure Range	Average Bubble Oscillation Frequency kHz	Number of Data Points*	Average Calculated Pressure mmHg	Average Catheter Pressure mmHg
−3 to −0.1	34.54	5,180	− 1	− 2.5
0.0 to 9.9	34.01	1,730	−11	2.0
10.19 to 10.9	35.94	761	27	17.0
20 to 24.9	36.15	1,660	31	22.2
25 to 30.9	36.19	1,778	32	27.0
31 to 39.9	36.04	1,852	29	35.3
40 to 51.9	36.66	931	41	45.5

*Each point represents the average of more than 100 discrete bubble oscillations.

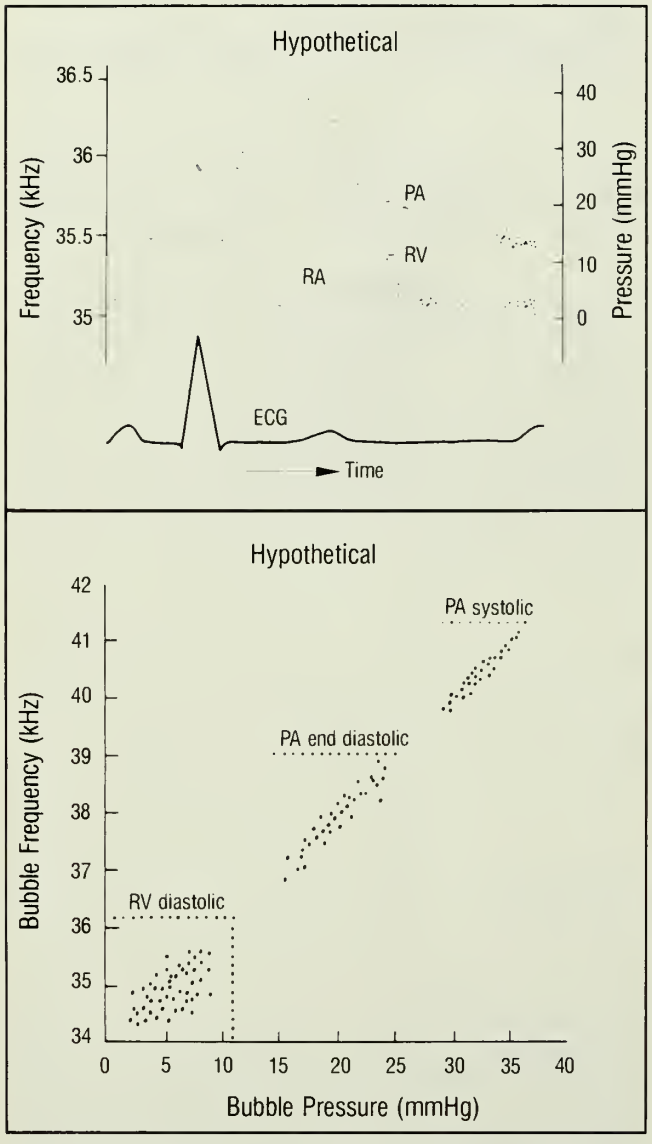

Figure 3.—Illustration of hypothetical data showing idealized frequency of bubble oscillation (corresponding to pressure) versus time relative to the electrocardiogram (ECG), with microbubble oscillations recorded from all right-sided heart chambers (upper panel). The lower panel displays grouped data derived from bubble ultrasonic ringing frequency for converting pressure with labels on areas assumed to represent right ventricular (RV) and pulmonary artery (PA) pressure levels.

infused through the catheter in the superior vena cava and the ultrasonic microphone was handheld over the anterior wall of the right ventricle. Following conclusion of the multiple infusions, the dogs were killed by barbiturate overdose.

Results

Data for one animal only will be presented for illustration of the technique. A total of 20 microbubble injections were carried out with right ventricular systolic and diastolic pressures varying from 16/−3 to 51/0 mm of mercury. Right ventricular pressures were first elevated by peripheral infusions of prostaglandin $F_{2\alpha}$. Right ventricular pressures rose from a baseline of 22/−3 mm of mercury to a peak of 30/−2 mm of mercury with a maximum prostaglandin infusion rate of 5 mg per minute. Heart rates were persistently in the 150 to 160 beats-per-minute range during the prostaglandin infusion. Subsequent elevations of the right ventricular pressure were reliably obtained by partial obstruction of the proximal pulmonary artery with finger pressure. The aortic pressure did not change significantly with either intervention.

A summary of the average catheter pressures, corresponding microbubble oscillation frequencies and derived pressures is presented in Table 1. From 100 to 1,000 discrete signal measurements were averaged to give an "individual" frequency for comparison with the pressure recorded simultaneously. The catheter pressure-bubble frequency and catheter pressure-bubble estimated pressure data using "individual" data points are plotted (Figures 5 and 6). Linear-regression analysis of the right ventricular transducer pressure versus this microbubble oscillation frequency result yields a correlation coefficient of .77 and the standard error in derived pressure was ± 14 mm of mercury using individual data.

Discussion

We first reported the use of pressurized microbubbles to determine cardiac pressures in an in vivo model in 1981.[10] The present data only show the principle and feasibility of using microbubble oscillation signals for determining right-

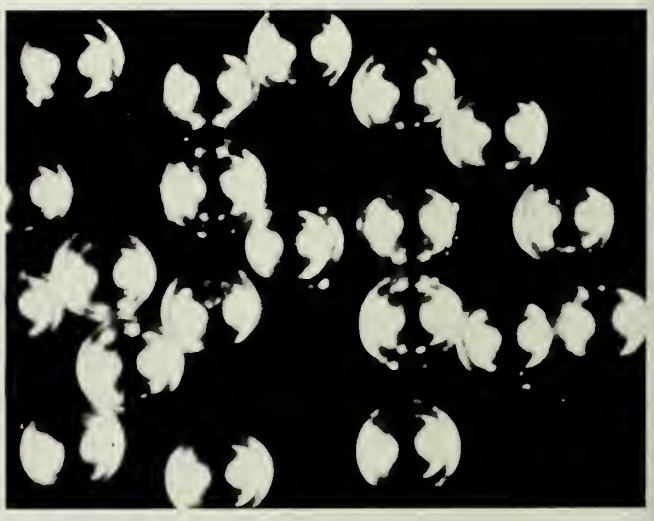

Figure 4.—Photomicrograph of the encapsulated microbubbles. Note their size uniformity. The bubbles are consistently contained in the center of the saccharide shell. The individual spheres used in this work had a mean diameter of 144 microns and the bubbles have a mean diameter of 102 microns. (The photography results in a bright pair of reflections in each sphere.)

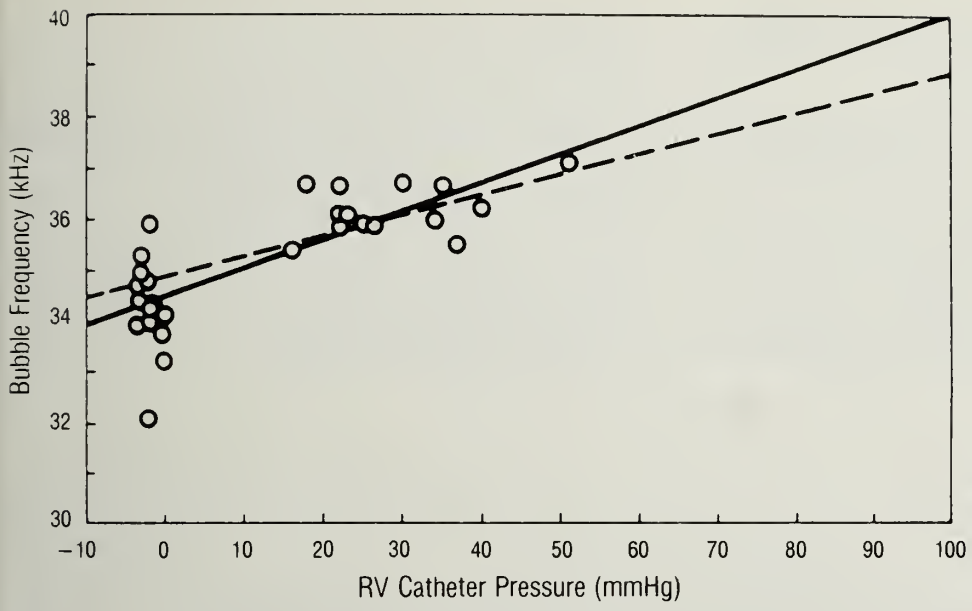

Figure 5.—Recorded bubble oscillation frequencies and corresponding right ventricular (RV) pressures as measured by solid-state manometer. These "individual" data points (see text) are expressed with the solid regression line and the dashed line expected from equation 3. Least-squares analysis: $Y = .055 \times X + 34.508$, $r = .7662$, c (constant) = 1.2.

sided heart pressures that may be developed for clinical use in the future. Significant research and development have been carried out using in vitro models, including a heart-lung model with pulsatile flow.[1] The standard error in derived pressures in the present work in dogs was greater than 10 mm of mercury, which is not sufficiently accurate for clinical use at this time. However, the results of this initial effort provide for optimism concerning the possible use of such material in an improved form.

Further refinements in the microbubble oscillation technique are needed. The current ultrasonic microphones were not built for our purpose, lack directionality and can be used only in open-chest procedures where the transducer can be positioned over the cardiac chamber or vessel of interest. Producing precision microbubbles is a major challenge for this technique and further developments in the mass production of these bubbles, as well as defining an optimal vehicle,

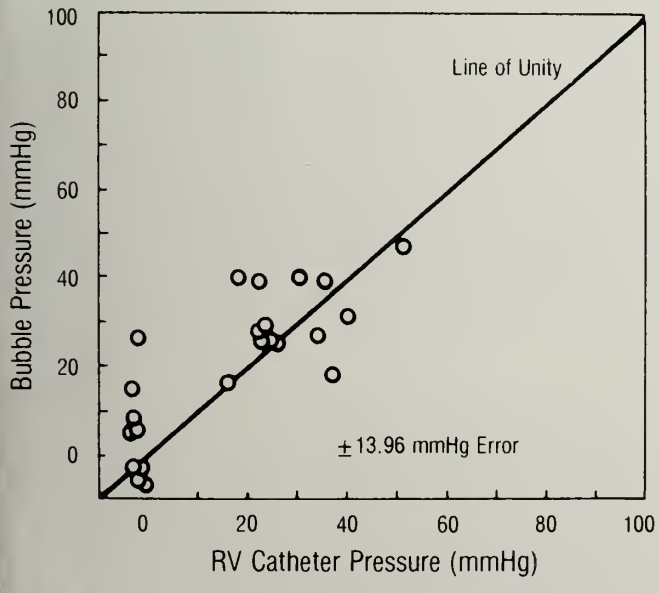

Figure 6.—Pressures derived from bubble oscillation and corresponding measured right ventricular (RV) pressures for "individual" data (see text).

are necessary. The vehicle must be designed to carry the microbubble material and protect it from dissolving until the material reaches the heart. Turbulence in the right side of the heart shears the vehicle away from the encapsulated microbubble and allows capsule dissolution and gas release. Delayed release will carry the bubble through the heart and into the pulmonary capillary bed without release from its capsule.

Modifications of both the microbubble material and the delivery by its vehicle are necessary so a maximum number of signals can be detected over several cardiac cycles. Toxicity studies are currently under way to analyze possible damage from either the microbubble material or the vehicle. Carbon dioxide has been chosen as the optimal gas for the pressurized microbubbles because of its short life in the circulation and its biologic compatibility.[11] Carbon dioxide bubbles that do not dissolve in the lungs will be filtered by the pulmonary capillary circulation.[12] Likewise, the lungs should serve as filters for the saccharide capsules in the unlikely event that they do not dissolve. Preliminary results indicate that no microscopic damage to the pulmonary capillaries or parenchyma occurs following multiple injections of the microbubble material.[1] There may be concern over the potential for injecting significant amounts of gas into the circulation; the volume of carbon dioxide, however, in each injection of 30,000 microbubble particles is about 0.07 ml of gas at 1 atm pressure.

There is a theoretic possibility that hemolysis could occur due to vibratory damage from the oscillating bubbles. Initial experience indicates that significant hemolysis does not occur when the microbubble material is fully diluted in the circulation at the time of bubble release in the right side of the heart.[1] Microscopic examination of the right ventricles of dogs receiving 10 to 100 times the standard amount of microbubble material has failed to show damage to the myocardium when studied one to three hours after infusions.[1]

The microbubble expansion technique provides an interesting approach to measuring intracardiac pressures. Much further work needs to be done before this could become a clinically testable technique. At present the potential for measuring higher—systolic—pressures seems more likely than for lower—diastolic—pressures. Even if acceptable accuracy

for lower pressures is not achieved, we can envision the possible use of the method as a screening tool for pulmonary hypertension.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Transmission of Disease Via Mouth-to-Mouth Resuscitation

QUESTION:

Is there a proved relationship between the use of mouth-to-mouth resuscitation and the transmission of communicable and infectious diseases?

OPINION:

In the opinion of the Scientific Advisory Panels on Emergency Medicine, Internal Medicine and Preventive Medicine and Public Health, there is no proved relationship between the use of cardiopulmonary resuscitation (CPR) training mannequins and the transmission of communicable and infectious diseases. The American Heart Association, American Red Cross and the Centers for Disease Control concur that, if recommended mannequin decontamination procedures are followed and precautions are taken to prevent CPR students with known infectious oral, facial cutaneous of respiratory disease from participating in mouth-to-mannequin practice, the risk of the spread of communicable disease is extremely small.

The larger question whether actual mouth-to-mouth resuscitation is likely to transmit a communicable disease is difficult to answer. Since diseases such as the acquired immunodeficiency syndrome (AIDS), mononucleosis, herpes simplex and hepatitis B are known to be or have the potential to be transferred by saliva, it is theoretically possible that mouth-to-mouth resuscitation can transmit communicable disease.

In spite of the widespread use of CPR training mannequins and actual mouth-to-mouth cardiopulmonary resuscitation in recent years, the risk of disease transmission appears to be minimal. Since most resuscitative efforts take place in health care institutions, however, it is prudent to have other means of resuscitation available.

Decreasing Incidence of Gonorrhea in Homosexually Active Men—Minimal Effect on Risk of AIDS

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The incidence of gonorrhea in homosexually active men in Seattle-King County and in Washington State as a whole decreased by 57% from 1982 to 1984, compared with a 20% decrease among heterosexual men and women. This probably reflects behavioral changes of homosexual men in response to the epidemic of the acquired immunodeficiency syndrome (AIDS). Nevertheless, changes in sexual behavior that greatly reduce the incidence of gonorrhea do not necessarily result in a similar reduction in the risk of exposure to the virus that causes AIDS.

(Handsfield HH: Decreasing incidence of gonorrhea in homosexually active men—Minimal effect on risk of AIDS [Clinical Investigation]. West J Med 1985 Oct; 143:469-470)

In recent reports decreasing incidences of gonorrhea have been documented among homosexually active men in Denver[1] and New York,[2] attributed to behavioral changes in response to the epidemic of the acquired immunodeficiency syndrome (AIDS). This report contains additional evidence for this phenomenon, based on the reported rates of gonorrhea in Washington State and the state's largest sexually transmitted diseases (STD) clinic system.

Methods

Reported cases of gonorrhea from 1982 through 1984 in Washington State and among patients attending the STD clinics of the Seattle-King County Department of Public Health were analyzed according to sexual orientation or anatomic site of infection. For patients attending the STD clinics, sexual orientation is routinely recorded. Gonorrhea as a percentage of clinic visits was calculated using total visits (initial diagnosis or follow-up) for each patient group. Gonorrhea in Washington State is recorded by anatomic site of infection; specific data on sexual orientation are not available. The Seattle-King County STD clinic cases are included in the statewide data.

Results

The incidence of gonorrhea in homosexually active men attending the Seattle-King County STD clinics fell 57% from 1982 to 1984, compared with decreases of 20% in heterosexual men and women (Table 1). The decreases were partly attributable to a decline in clinic attendance for heterosexuals but not for homosexual and bisexual men. The statewide trends for reported rectal and urethral infections in men and cervical gonorrhea in women mirrored the STD clinic incidences. (Urethral infections reflect gonorrhea in men of either sexual orientation.) During the course of this study, reported AIDS cases in Washington rose from 14 through 1983 to 69 in 1984; 25 more cases were reported in the first four months of 1985 (total, 108 cases to date, of which 78 occurred in Seattle-King County).

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
STD = sexually transmitted diseases

Discussion

It is probable that the declining incidence of gonorrhea in homosexually active men reflects changes in sexual behavior in response to publicity about AIDS and perhaps to educational programs focusing on AIDS risk reduction. Greater attendance for health screening examinations, also engendered by the fear of contracting AIDS, may be an additional contributing factor. Anecdotal reports from homosexually active men in King County and their health care providers support both of these interpretations. The more modest decrease in gonorrhea in heterosexual men and women is similar to the national trend and may be due to demographic factors (de-

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TABLE 1.—*Reported Cases of Gonorrhea According to Sex and Sexual Orientation or Site of Infection, 1982-1984*

Reporting Source	Sex	Sexual Orientation or Site of Infection	Parameter	Year 1982	Year 1983	Year 1984	Percent Change 1982-1984
Seattle-King County STD Clinics	M	Homosexual or Bisexual	No. cases	738	499	320	−57
			Clinic visits*	5,137	5,184	4,840	− 6
			Percent†	14.4	9.6	6.6	−54
	M	Heterosexual	No. cases	1,096	985	876	−20
			Clinic visits*	16,264	14,348	14,009	−14
			Percent†	6.7	6.9	6.3	− 6
	F	Heterosexual	No. cases	692	626	556	−20
			Clinic visits*	12,795	11,022	9,873	−23
			Percent†	5.4	5.7	5.6	+ 4
Washington State . . .	M	Rectum	No. cases	598	394	257	−57
	M	Urethra	No. cases	5,373	4,577	4,176	−22
	F	Cervix	No. cases	4,528	4,061	3,898	−14

STD=sexually transmitted diseases

*Clinic visits includes attendance for a new disease episode, screening or follow-up.
†Percent refers to gonorrhea cases as a percentage of total visits to the STD clinics for each group of patients.

clining number of persons aged 15 to 30 years); gonorrhea screening and other control measures, or, as for homosexual men, an enhanced fear of contracting STD, especially genital herpes.[3]

Although these results reflect a desirable trend, data from San Francisco[4,5] and Chicago[6] suggest that only modest changes have occurred in the sexual behavior of homosexual men. A moderate reduction in the number of sexual partners or increased attendance for health screening examinations may result in a large change in the incidence of gonorrhea without materially affecting the risk of AIDS virus exposure. For example, in Seattle about a third of homosexual and bisexual men attending the Seattle-King County STD clinic have serologic evidence of AIDS virus infection; a 90% reduction in the number of anonymous partnerships from 50 to 5 contacts annually would confer a decrease in the risk of AIDS virus exposure from virtually 100% only to 87%. The AIDS risk-reduction guidelines of the Seattle-King County Department of Public Health advise men to abstain from all sexual activity with other men or limit homosexual contact to permanent monogamous relationships. Casual homosexual partnerships are strongly discouraged, even in the context of "safe" sex practices intended to reduce the exchange of blood or secretions.

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'Pseudoseptic' Arthritis in Patients With Rheumatoid Arthritis

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It is generally recognized that patients with rheumatoid arthritis are at greater risk than the general population for the development of bacterial joint infection. It is not usually appreciated, however, that such patients may present with a clinical syndrome that mimics septic arthritis in most respects except that all cultures are consistently negative and antibiotics are not essential for treatment. We report our experience with five cases of "pseudoseptic" arthritis in patients with rheumatoid arthritis and suggest an approach for management.

(Call RS, Ward JR, Samuelson CO Jr: 'Pseudoseptic' arthritis in patients with rheumatoid arthritis. West J Med 1985 Oct; 143:471-473)

Patients with rheumatoid arthritis are at greater risk for bacterial infection of joints than the general population.[1-5] Certainly when a patient presents with disproportionate pain and swelling in one or more joints, especially if accompanied by the abrupt onset of systemic features such as fever and chills, the primary objective is to exclude an infectious process. The early correct diagnosis of joint infection in patients with rheumatoid arthritis may be difficult because both the preexisting joint disease and the anti-inflammatory drugs used in treatment may obscure or alter the presentation of the joint infection. In addition, more than one joint can be infected. Thus, the clinical presentation of septic arthritis in patients with rheumatoid arthritis may be atypical or incomplete.

We have recently seen five patients with rheumatoid arthritis who presented with clinical and laboratory findings that were highly suggestive of bacterial infection of the joints, but synovial fluid and blood cultures were sterile. These patients were admitted to hospital and two were given extended antibiotic treatment for "culture-negative septic arthritis." We now recognize a clinical syndrome in such patients that mimics septic arthritis. We here report these observations and suggest an approach to management.

Patients

Five patients with classical rheumatoid arthritis are included in this description. For illustrative purposes, two brief patient reports (cases 1 and 3) are presented.

Case 1

The patient, a 29-year-old man with rheumatoid arthritis of 14 years' duration, was admitted to hospital with a history of fever and acute painful swelling of the left knee for 24 hours. His oral temperature was 38.3°C (100.9°F). On general physical examination there were no remarkable findings except for the changes of rheumatoid arthritis. His left knee was swollen, erythematous and had a palpable effusion in addition to significant synovitis. The synovial fluid nucleated cell count was 35,000 per μl with 89% polymorphonuclear leukocytes (PMNs) and the glucose concentration was 10 mg per dl. A Gram's stain and polarized microscopy for crystals were negative. A presumptive diagnosis of bacterial infection of the joint was made and treatment with parenteral nafcillin sodium and cefazolin sodium, as well as supplemental prednisone, was instituted. The fever resolved within 24 hours and the joint pain, swelling and warmth abated. Despite the absence of bacterial growth in cultures of synovial fluid and blood, antibiotic treatment and daily needle drainage of the knee were continued, and the cultures were consistently negative for bacterial growth. After 21 days of antibiotic treatment, the blood leukocyte count dropped to 2,700 cells per μl with 3% PMNs. Leukopenia due to nafcillin therapy was suspected and the antibiotic therapy was discontinued. He continued to do well and was discharged from hospital when his leukopenia resolved.

Four months later he was readmitted with fever, chills and pronounced swelling, tenderness, warmth and erythema of the

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left knee. The results of a physical examination were not changed from his previous admission findings. The synovial fluid nucleated cell count was 50,000 cells per μl with 91% PMNs and a glucose concentration of 6 mg per dl. Despite a Gram's stain that showed no bacteria, a regimen of parenteral gentamicin sulfate and cefazolin was initiated along with an increase in the prednisone dosage from 4 mg a day to 20 mg a day. Within 48 hours, he was afebrile and the acute arthritis of the left knee had resolved. The synovial fluid nucleated cell count was 34,000 cells per μl with 81% PMNs. The antibiotic therapy was discontinued and he has shown no evidence of infection in 48 months of observation.

Case 3

The patient, a 37-year-old man with rheumatoid arthritis of ten years' duration, had a three-week generalized "flare" in his joint disease. He was admitted to hospital with a 24-hour history of severe redness, heat, swelling and pain in both wrists associated with rigors and fever. His only therapy was the administration of naproxen, 750 mg a day. On physical examination there was synovitis of several joints, rheumatoid nodules and both wrists were erythematous, warm, swollen and extremely tender. His oral temperature was 37.7°C (99.9°F). The synovial fluid from the wrist had 98,000 nucleated cells per μl with 88% PMNs and a glucose concentration of less than 10 mg per dl. Crystals were not found and a Gram's stain was negative. Synovial fluid cultures were done for *Neisseria*, aerobic and anaerobic bacteria, mycobacteria and fungi. Conventional blood cultures were done. The peripheral blood leukocyte count was 13,000 cells per μl with 33% PMNs.

There was no evidence for an associated infection by history or physical examination and he was given nafcillin parenterally. Within 24 hours he was afebrile, his acute arthritis in the wrists abated and cultures of synovial fluid yielded no growth. Antibiotic therapy was discontinued, he remained well, except for his rheumatoid arthritis, and was discharged from hospital.

Three months later, he had a shaking chill and presented with the abrupt onset of painful swelling in his right wrist. On physical examination, findings of generalized rheumatoid arthritis were unchanged except for warmth, pronounced swelling and severe tenderness and pain of the right wrist. A synovial fluid specimen from the wrist had a nucleated cell count of 129,000 cells per μl with 90% PMNs. No crystals were seen on polarized microscopy and a Gram's stain was negative. Nafcillin and gentamicin were given and within 24 hours the acute arthritis in the wrists resolved. When cultures of synovial fluid and blood specimens showed no growth, the antibiotic regimen was discontinued and he was discharged. He has remained well except for his chronic rheumatoid arthritis for 54 months.

Comments

Five patients with rheumatoid arthritis had one or several episodes of acute inflammation in one or more joints that were associated with fever, chills or both in four cases (Table 1). The duration of illness was from 12 to 48 hours when initially evaluated. Large joints involved in decreasing frequency were the knees, wrist, ankle, elbow and shoulder. The peripheral joints of the hands and feet were not noted to be unusually inflamed in these patients.

All patients had substantial tenderness, painful motion and an effusion in the involved joint. Erythema or warmth of the involved joint or both were recorded in six of ten episodes and systemic fever was present in seven. Peripheral blood leukocytosis was usually present and, when measured, the Westergren erythrocyte sedimentation rate was elevated.

The synovial fluid findings were impressive, with nucleated cell counts of greater than 50,000 cells per μl in all but one instance. A notable preponderance of PMNs was also seen except in one patient (patient 2) whose synovial fluid nucleated cell count was 96,400 cells per μl (Table 1). Crystals were not identified in the fluids and a Gram's stain was negative in all. Cultures failed to yield growth of bacteria, mycobacteria and fungi in all patients. The synovial fluid glucose concentration was often greatly decreased.

In all patients, there was a rapid resolution of the acute joint symptoms. This response is difficult to assess because increased doses of prednisone were given in six episodes. On the basis of a presumptive diagnosis of bacterial infection of the joint, antibiotics were given for eight of the ten episodes. In two patients, these were continued for two weeks or longer despite negative synovial fluid and blood cultures. In the other patients, the antibiotic therapy was promptly stopped when synovial fluid cultures showed no growth. In two episodes, antibiotic treatment was withheld pending positive cultures.

A review of these patients failed to elicit a cause for the

TABLE 1.—*Selected Clinical and Laboratory Variables in Patients With Rheumatoid Arthritis Who Were Admitted With the Diagnosis of Bacterial Infection of Joints*

Patient	Age yr	Sex	Episode	Admission Temperature °C	Peripheral Leukocyte Count per μl	ESR mm/hr	Rheumatoid Factor Titer	Synovial Fluid Findings: Nucleated Cell Count per μl	Synovial Fluid Findings: % PMNs	Synovial Fluid Findings: Glucose mg/dl
1	29	♂	1	38.3	11,400	53	1:320	35,000	89	10
			2	38.5	11,100	39		50,000	91	6
2	65	♂	3	37.0	19,300	ND	1:320	395,000	94	13
			4	38.4	11,600	ND		96,400	73	60
			5	38.5	20,000	70		60,000	90	<10
			6	35.6	18,000	123		113,000	88	ND
3	37	♂	7	37.7	13,000	33	1:320	98,000	88	6
			8	36.7	8,600	ND		129,000	90	ND
4	64	♂	9	37.3	24,700	ND	1:1280	89,000	97	ND
5	69	♀	10	37.3	7,900	56	1:40	52,000	92	ND

ESR=erythrocyte sedimentation rate, ND=no data, PMNs=polymorphonuclear leukocytes

abrupt flare in the involved joints. All had classical, seropositive, nodular rheumatoid arthritis. None of these patients had clinical evidence of concomitant bacterial, viral, mycobacterial or fungal infections. The possibility of gonococcal arthritis was not considered likely as all patients and their marital partners denied extramarital sexual activity. Furthermore, there were no symptoms or signs of urethritis, cervicitis or skin lesions, and while cervical, urethral, rectal and throat cultures were not done on Thayer-Martin media, synovial fluid cultures on chocolate agar uniformly failed to yield growth of *N gonorrhoeae*. While synovial biopsies to exclude mycobacterial or fungal infection were not done, the clinical presentation, negative synovial fluid cultures for mycobacteria and fungi and the subsequent clinical course of the patients exclude these diagnoses. No crystals were seen in any of the synovial fluids and all patients had normal serum uric acid concentrations. Patient 1 has been followed for more than four years and the other patients for at least three years without evidence of disease other than rheumatoid arthritis.

Discussion

In five patients with seropositive classical rheumatoid arthritis of long duration, we observed ten episodes of acute monarticular or oligoarticular flares that were initially considered to be bacterial infection of the joint(s). Cultures of synovial fluid and blood, however, yielded no growth and there was rapid resolution of the arthritis that appeared to be independent of antibiotic treatment. Thus, we propose that patients with rheumatoid arthritis can present with clinical and laboratory features that mimic bacterial joint infections and we have termed this syndrome "pseudoseptic arthritis."

The usual approach to these patients is to look for an associated infection or portal of entry. Appropriate cultures as indicated by these findings are done. Cultures of blood specimens are obtained and synovial fluid analysis for total and differential cell counts, crystals, glucose content and cultures for *N gonorrhoeae*, aerobic and anaerobic bacteria, mycobacteria and fungi is considered. A Gram's stain on the centrifuged fluid specimen is examined and appropriate antibiotics are given immediately based on the most likely infecting organism. When there is no evident portal of entry or concomitant systemic bacterial infection and a Gram's stain of the synovial fluid is negative, broad-spectrum antibiotic therapy is implemented if the synovial fluid nucleated cell count is high and there are greater than 90% PMNs. This approach seems reasonable in acutely ill or severely debilitated patients.

At its inception, bacterial infections of joints most often result from hematogenous seeding of the synovium. This tissue infection ultimately spreads to the joint space.[6] Thus, early infection cannot be excluded by an absence of bacterial growth from synovial fluid culture and repeated daily or more frequent synovial fluid aspiration and cultures must be done to determine infection. Faced with the dilemma of the clinical impression of bacterial joint infection, a negative synovial fluid Gram's stain and no identifiable portal of entry, antibiotic treatment is usually started immediately. Treatment is then continued pending culture results and the response of the arthritis. In the setting of no growth from cultures and rapid clinical improvement, the antibiotic regimen might be discontinued. Careful further observation is then required to ensure that incompletely treated bacterial arthritis is not present, while considering "pseudoseptic arthritis" as a likely explanation.

A major problem with this approach is to define response in a joint with preexistent rheumatoid synovitis. Successful treatment of bacterial infection of a joint is measured by rapid eradication of the infective agent as indicated by negative synovial cultures, whereas a decrease in arthritis, total synovial fluid and total leukocyte and polymorphonuclear cell counts may not be observed for up to seven or more days of treatment.[7]

An alternative approach is to consider that "pseudoseptic arthritis" could be present. If the Gram's stain of synovial fluid is negative and the patient does not have an identifiable portal of entry, concomitant infection (pneumonia, urinary tract infection and so forth), an immunocompromised state (high-dose steroids, cytotoxic or immunosuppressive drug therapy) or features of bacterial sepsis, antibiotic treatment might be delayed pending the results of synovial fluid cultures. A decision of "not to treat" is easier if a patient has had previous episodes of culture-negative arthritis. Thus, a physician will be able to avoid the use of prolonged antibiotic treatment usually recommended for nongonococcal bacterial arthritis. Conversely, if an organism is ultimately found, selective therapy can be devised. Furthermore, the adequacy of treatment can be assessed by determining serum or synovial fluid antibiotic bactericidal levels and by repeated monitoring of synovial fluid for response to therapy by disappearance of the organism in synovial fluid cultures. Based on available evidence, a delay of two to five days *early* in the course of bacterial infection of joints would not influence an ultimate successful result.[7] If the severe monarthritis or oligoarthritis persists, a repeated search for infection, including joint fluid analysis, should be diligently pursued.

The pathogenesis of this syndrome remains unexplained. As this was a retrospective study, synovial fluid counterimmunoelectrophoresis was not done, nor were bacterial peptidoglycans or microbial antigens in synovial fluid or antibodies to bacterial antigens sought.[8] While all of the patients had classical rheumatoid arthritis, there were no unique features such as vasculitis. They did not exhibit the typical rash of adult Still's disease, nor did they have lymphadenopathy, splenomegaly or other systemic manifestations.

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Sexual Potency Before and After Radical Prostatectomy

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A triad of factors can favorably influence the maintenance of sexual potency after radical prostatectomy: the surgical avoidance of cavernous neurovascular bundles, the preoperative interest of the surgeon in broaching the subject with the patient and the continued encouragement given the patient by his attending physician as to probable preservation of sexual competency following the surgical procedure.

(Finkle AL, Williams RD: Sexual potency before and after radical prostatectomy. West J Med 1985 Oct; 143:474-475)

Recent reports of preserved sexual potency after radical prostatectomy[1,2] contrast substantially with previous conclusions as to invariable loss.[3,4] To establish a baseline for postoperative sexual function, we obtained a sexual history of each patient before the operation. Herein we report our findings regarding preoperative and postoperative sexual function in 41 patients who underwent pelvic node dissection and radical prostatectomy for prostatic adenocarcinoma between October 1979 and August 1984. Our purpose is twofold: to encourage the development of protocols for evaluation and to stimulate publication of the data thus acquired to improve knowledge of postprostatectomy sexual potency.

Patients and Methods

From October 1979 through July 1984, 41 radical prostatectomies were done by one of us (R.D.W.) or by urology residents under his supervision at the University of California, San Francisco, School of Medicine or the San Francisco VA Medical Center. In all patients, pelvic lymph node dissection was carried out before the prostatic operation. If no malignancy was found in a frozen section study, a radical retropubic prostatectomy was done immediately (38 patients). In the three other patients, microscopic examination of the frozen section indicated a high probability of nodal metastatic spread, and a radical perineal prostatectomy was done.

Before the 1983 report by Walsh, Lepor and Eggleston[2] of their surgical technique for preserving certain neurovascular bundles (and, thus, sexual potency), our efforts to ablate the adenocarcinoma were undertaken without clear regard for preserving potency. Subsequently, in all instances we used a Walsh retropubic surgical approach designed to spare potency as well as to excise the malignant tumor.

Our evaluation of the patients' postoperative sexual potency was initially attempted by a mailed questionnaire (1979 to 1981). In view of the considerable interest of the respondents, many of whom requested an interview, we elected to arrange a personal meeting or at least a telephone contact. In this retrospective study (1979 to 1981), the patient was interviewed alone and the findings were compared with those obtained from husband and wife together. No appreciable differences were noted from the solo or two-partner interviews, although the latter would probably tend to produce more accurate reports.

From 1979 to 1981, penile erection was accepted as evidence of intact "potency," as had been necessary in the study of Finkle and Taylor,[1] who were obliged to review hospital records in their retrospective study of sexual potency after radical prostatectomy. Only two of our patients reported erections, but they were unable to engage in sexual intercourse. Therefore, we abandoned this definition.

From 1981 to 1984, in the prospective phase of this study, we encountered more men who reported penile erection and ability to carry out intercourse. Therefore, we upgraded our definition to mandate coital competence as evidence of preserved sexual potency.[5] This definition proved appropriate in light of the vastly increased incidence of sexual potency in our patients after we applied the Walsh method for radical retropubic prostatectomy.

Results

Of our 26 patients who underwent radical prostatectomy between October 1979 and April 1983, one was impotent preoperatively and remained so postoperatively; of the 25 who were potent preoperatively, only 2 (8%) professed "partial erections" after their operations, and 21 became impo-

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tent. (Two men died of nonmalignant causes within three months of the operation, not having attempted intercourse.)

In contrast, among the 15 patients who underwent radical prostatectomy after April 1983 in whom a specific attempt was made to preserve the periprostatic neurovascular bundles,[2] 6 of 10 (60%) who were potent preoperatively remained so postoperatively. Five patients who were impotent preoperatively remained so postoperatively.

Discussion

When men are advised of prostatic cancer, most are primarily concerned with optimal treatment of the cancer—a consideration that understandably supersedes the threat of sexual impotence. For many years, we had avoided intensive preoperative questioning of patients about their sexual status on the premise that these queries alarmed patients and made them worry about loss of potency, perhaps initiating a self-fulfilling prophecy.[6] For the same reason, no preoperative electronic monitoring tests, such as those devised by Scott and co-workers[7] or cited by Morgan and Pryor,[8] were done. It proved noteworthy to the interviewer (R.D.W.), however, that the patients evaluated for the present report were very appreciative of the time and consideration devoted by the urologic surgeon to the possible effect of the operation on sexual function and the potential preservation of sexual potency postoperatively. We recommend, therefore, that questioning as to sexual potency be introduced casually during the evaluation of marital status in the customary history elicited by clinicians.

For five decades after Young introduced radical prostatectomy in 1905,[9] it was generally assumed that postoperative sexual impotence was inevitable. The validity of this assumption was questioned by Finkle and Saunders[10] in 1960 and again by Finkle and colleagues[11] in 1975. More recently, these authors[12] noted that urologic counseling effected prompt reinstatement of sexual potency in 75% of 388 private patients, including some men who had had a radical prostatectomy.

The 1983 report by Walsh and associates[2] of their surgical technique for preserving sexual potency during radical prostatectomy has given renewed impetus to the treatment of prostatic cancer by radical surgical procedures. Their method of preserving the periprostatic cavernous neurovascular bundles in retropubic prostatectomy doubtlessly constitutes the fundamental basis for preservation of potency. As early as 1975, however, the preservation of sexual potency in response to urologic counseling alone was reported in six of ten private patients who had undergone radical perineal prostatectomy by one surgeon over a period of many years.[11] At that time, eight years before publication of the Walsh technique, it was obviously impossible knowingly to avoid operative damage to cavernous neurovascular bundles. Thus, if injury to these vital blood and nerve conduits had been avoided, it was pure happenstance; therefore, preoperative and postoperative encouragement by the urologist before 1975[11] and 1983[2] constituted the presumptive factor in reinstatement of sexual potency.

From these various considerations it appears that, in addition to the verifiable benefits of the Walsh technique of radical prostatectomy, preoperative and postoperative evaluations of sexual function by a tactful interview are valuable. Such inquiry by a urologist is appreciated by patients and undoubtedly represents positive reinforcement of ability to resume sexual intercourse after the operation—generally within several months to one year.

All surgeons who propose operations that may threaten sexual function should evaluate potency. One of us (R.D.W.) recently encountered two patients who had undergone radical cystectomy (including urethrectomy in one) who remained potent. These results are probably explained entirely by the intentional preservation of cavernous neurovascular bundles during the operation.

Should a patient doubt the successful resumption of coitus, especially a patient undergoing radical prostatectomy, the surgeon should consider the various factors cited in our experience: preoperative evaluation of sexual competence, intraoperative sparing of periprostatic neurovascular bundles and ongoing reassurance by the surgeon.

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Clinical Review

Menstrual Dysfunction in Pathophysiologic States

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The menstrual cycle is a complex entity involving many interactions of the central nervous system, hypothalamus, pituitary and ovaries. Normal menstrual function depends on a pulsatile gonadotropin-releasing hormone secretion leading to a pulsatile luteinizing hormone and follicle-stimulating hormone secretion that stimulates the ovaries. A cyclic burst of luteinizing hormone is also required for ovulation. Certain pathophysiologic states, such as those produced by stress, exercise and drugs, have the potential to affect the cycle at many levels. Chronic illnesses may have effects on β-endorphins and hypothalamic functioning. Alternatively, the weight loss associated with chronic illness may alter estrogen metabolism, thus altering hypothalamic or pituitary function. Anorexia nervosa and simple weight loss may have effects at the hypothalamic level or through altering estrogen metabolism, as well.

(Neinstein LS: Menstrual dysfunction in pathophysiologic states [Clinical Review]. West J Med 1985 Oct; 143:476-484)

During the past 20 years, many pathophysiologic states associated with menstrual dysfunction have increased in prevalence. An ever-enlarging number of women participate in strenuous athletics with a reported prevalence of menstrual dysfunction as high as 50%.[1] Anorexia nervosa, an increasingly common eating disorder, is associated with an almost 100% prevalence of amenorrhea.[2] Drug abuse, especially heroin use, is associated with a prevalence of amenorrhea of more than 90%.[3] As patients with chronic illnesses, such as chronic renal failure, systemic lupus erythematosus and cystic fibrosis, survive longer, menstrual dysfunction is becoming a significant problem.[4] In this article I examine the prevalence of menstrual dysfunction and recent research in the alterations that occur in the hypothalamic-pituitary-ovarian axis in these conditions.

To understand menstrual dysfunction, it is essential to have an appreciation for menarche and the normal menstrual cycle. Menstrual function has been reviewed in detail elsewhere[5-7] but a brief overview is given here.

Menarche and Puberty

Puberty is characterized by an acceleration of weight and height growth velocities and the appearance of secondary sexual characteristics. Menarche occurs as a result of an adolescent's rising and fluctuating estrogen levels. The pubertal period is characterized by the following several hypothalamic changes[8]:

- During early puberty, luteinizing hormone (LH) secretion dramatically increases predominantly in a pulsatile fashion, with higher levels at night. During late puberty and adulthood, pulsatile LH secretion occurs in high levels throughout the day and night.
- A decrease in the negative feedback sensitivity of the hypothalamus to estradiol and testosterone occurs, resulting in higher levels of LH and follicle-stimulating hormone (FSH).
- A positive feedback system develops in women so that critical levels of estradiol trigger a burst of gonadotropin-releasing hormone (GnRH) and LH.

The pulsatile nature of LH secretion is dependent on the pulsatile secretion of GnRH from the hypothalamus, which in turn may be controlled by a neural oscillator.[9] This pulsatile secretory pattern seems essential for normal reproductive function. For example, puberty can be induced in rhesus monkeys and in humans with Kallmann's syndrome using pulsatile GnRH.[9] Menses can be restored in women who have hypothalamic amenorrhea by giving low doses of GnRH secreted in a pulsatile fashion.[10]

The exact trigger of puberty with the associated hypothalamic pituitary changes is unknown. Postulated mechanisms include a genetic neurologic clock and triggers outside the central nervous system such as body composition.[11] A great deal of emphasis has been placed on the effect of body composition and percent of body fat on menarche.[12-15] In these

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone

studies, menarche occurs at about 17% body fat with at least 22% body fat required to maintain or restore menstruation.[15] However, these studies are limited by the fact that most involve indirect measurements of fat.[16] In addition, many other factors have been shown to be associated with age of menarche, such as race, socioeconomic status and distance from the equator.[16,17]

Menses

The menstrual cycle can be best understood by examining the ovarian phases.

Follicular Phase

Under the influence of pulsatile FSH and LH, ovarian follicles are stimulated to mature, leading to rising levels of estradiol.

Ovulatory Phase

In response to rising estradiol levels, a midcycle LH surge initiates ovulation. A mature follicle releases an ovum, leaving behind a functioning corpus luteum.

Luteal Phase

The corpus luteum secretes progesterone and estrogen, suppressing FSH and follicular growth. Without fertilization, involution of the corpus luteum occurs and estradiol and progesterone levels fall, resulting in menses and increasing levels of LH and FSH.

For regular menstrual function, pulsatile GnRH, pulsatile and cyclic LH secretion and ovarian secretion of estradiol and progesterone are all essential. The effects of various pathophysiologic states on menses and the hypothalamic pituitary ovarian axis will now be discussed.

Menstrual Dysfunction and Athletic Women

Women are increasingly involved in serious endurance sports. In the 1970 New York City Marathon, one woman started but did not finish. In the 1980 New York Marathon, 2,578 women started and 1,621 finished.[18] There are currently 6 million serious female runners in the United States and a third of high school athletes are female.[19] Concern is growing about the effects of vigorous exercise on gynecologic function.

Menstrual abnormalities have been reported in women engaged in middle- and long-distance running, swimming, rowing, tennis, field events and ballet.[20] The prevalence of menstrual dysfunction (amenorrhea, oligomenorrhea or both) in runners ranges from 6% to 43%[1,21-26] (see Table 1) and from 47% to 79% in ballet dancers.[27-30] Not only are menstrual irregularities common, but the age of menarche in athletes seems delayed (see Table 2). Except for those athletes who started training after menarche, the age of menarche is later than the population norm of 12.5 years, ranging from 13.7 to 15.4 years.[1,27-34]

Proposed factors predisposing female athletes to secondary amenorrhea include training intensity, body composition (weight loss and alteration of body fat), stress, nulliparity and prior menstrual function before training.[35]

Body Composition

Competitive athletes have less body fat than control populations. For example, competitive distance runners may have only 7% to 8% body fat, whereas recreational runners have 15.2% and mature nonathletic women 26% to 28%.[35] Many studies suggest that changes in body composition are highly correlated with the menstrual irregularities of athletes.[23,24,26,30,34-38] An example of this association is a study by Schwartz and co-workers showing greater weight loss and lesser weight and body fat in amenorrheic runners compared with a control population and normally menstruating middle-distance and long-distance runners (Figures 1 and 2).[36] Conversely, Feicht and associates found no difference in weight between 35 menstruating runners and 19 runners with amenorrhea.[1] Stager and associates also showed no difference in ponderal index between normal menstruating runners and runners who had oligomenorrhea.[39] In addition, in several studies of ballet dancers, menses returned with vacation or injury breaks without an associated weight change.[30,33,34,40]

TABLE 1.—*Prevalence of Menstrual Dysfunction in Athletes*

Study	Number	Type of Athlete	Women With Menstrual Dysfunction (%)
Runners			
Feicht et al, 1978[1]	128	Runners	6-43
Dale et al, 1979[21]	114	Joggers	23
		Runners	34
Baker et al, 1981[22]	23	Runners	39
Lutter and Cushman, 1982[23]	383	Runners	23
Sanborn et al, 1982[24]	237	Runners	26
Bloomberg,1977[25]	47	Long-distance runners	42
Shangold and Levine, 1982[26]	394	Marathon runners	24
Dancers			
Cohen et al, 1982[27]	30	Ballet	47
Calabrese et al, 1983[28]	29	Ballet	59
Abraham et al, 1982[29]	29	Ballet	79
Frisch et al, 1980[30]	89	Ballet	55

TABLE 2.—*Age of Menarche in Athletes*

Study	Number	Sport	Mean Age at Menarche (Years)
Ross et al, 1976[31]	15	Figure skaters	14
Feicht et al, 1978[1]	54	Runners	13.6
Malina et al, 1979[32]	139	Olympic athletes	13.7
Frisch et al, 1981[33]	21	Swimmers	15.0*
			12.6†
	17	Runners	15.2*
			12.9†
Warren,1980[34]	34	Ballet dancers	15.4
Frisch et al, 1980[30]	89	Ballet dancers	13.7
Cohen et al, 1982[27]	32	Ballet dancers	12.8†
Abraham et al, 1982[29]	29	Ballet dancers	14.8
Calabrese et al, 1983[28]	29	Ballet dancers	14.3

*Training began before menarche.
†Training began after menarche.

There is an alternative explanation to the relationship between body composition and menstrual dysfunction. It has been suggested by some that delayed menarche may lead to a more linear physique suitable for sports.[17] For example, Warren found that ballet dancers had a lower upper- to lower-body ratio and larger arm span to height difference (2.8 cm versus 1.2 cm) than their female siblings and mothers.[34] According to this theory, menstrual irregularities are more common in athletes because athletes are a select group. In other words, women with menstrual delay and irregularities develop a body better suited for athletics and, thus, choose athletics more often.

Training Intensity

Many studies have examined the correlation between intensity of physical training and the prevalence of amenorrhea, severity of menstrual dysfunction and age of menarche.* Several studies show a direct correlation in runners between the prevalence of amenorrhea and weekly training mileage (see Figure 3).[1,23,24,44] In Lutter and Cushman's study, the severity of menstrual dysfunction (eumenorrhea→oligomenorrhea→amenorrhea) increased as weekly mileage and days of running per week increased.[23] Abraham and colleagues found that in 19 of 21 ballet dancers, menstrual function improved after they stopped dancing for four weeks.[29] Two studies by Frisch and associates show later menarche with earlier onset of training.[30,33] Conversely, two other studies show no correlation between training intensity and menstrual dysfunction.[39,43] In one of these studies, however, few women ran more than 20 miles a week.[43]

Other Factors

In several studies there has been a high correlation between menstrual irregularities occurring before training and the prevalence occurring during training.[18,26,37,40] Shangold and Levine found that 93% of marathon runners with regular

*Reference numbers 1, 23, 24, 28, 33, 35, 41-44.

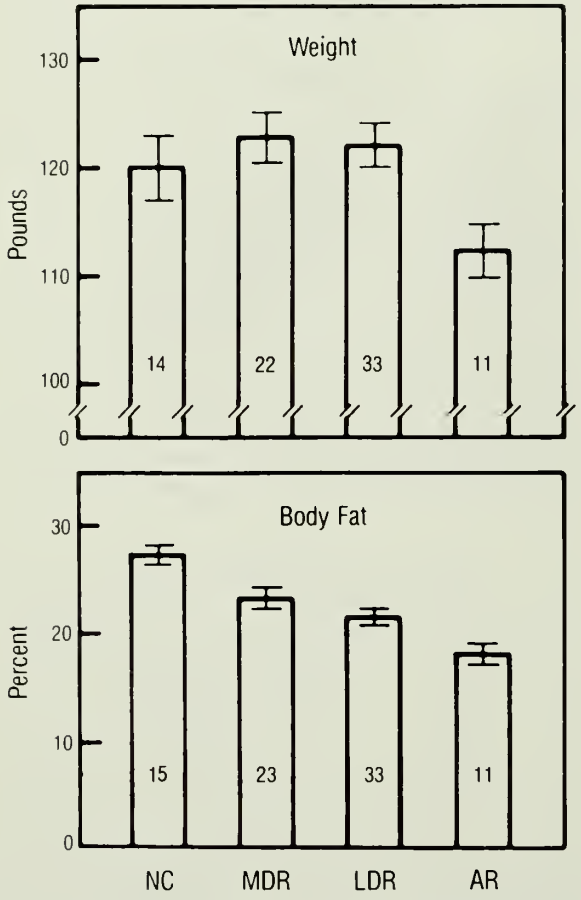

Figure 1.—Mean (± standard error) weights and percentage of body fats of women runners and nonrunners. The weight of women with amenorrhea (AR [amenorrheic runners]) is significantly less ($P<.05$) than that of the other groups (from Schwartz et al,[36] with permission from authors and publisher). NC = normal controls (nonrunners, normal menses); MDR = middle-distance runners with normal menses; LDR = long-distance runners with normal menses

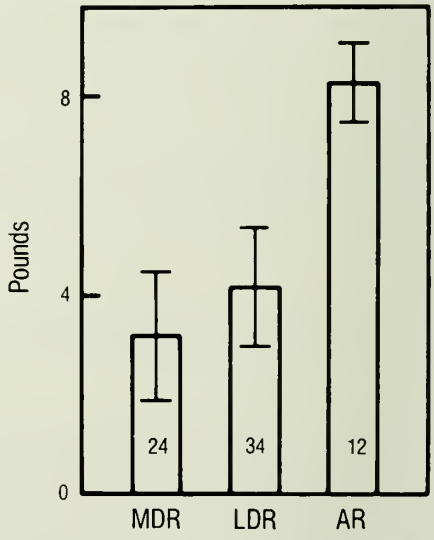

Figure 2.—Mean (± standard error) weight loss after the onset of running. Women with amenorrhea (AR [amenorrheic runners]) reported themselves to have lost significantly more weight ($P<.05$) than did women in other groups (from Schwartz et al,[36] with permission of authors and publisher). MDR = middle-distance runners with normal menses, LDR = long-distance runners with normal menses

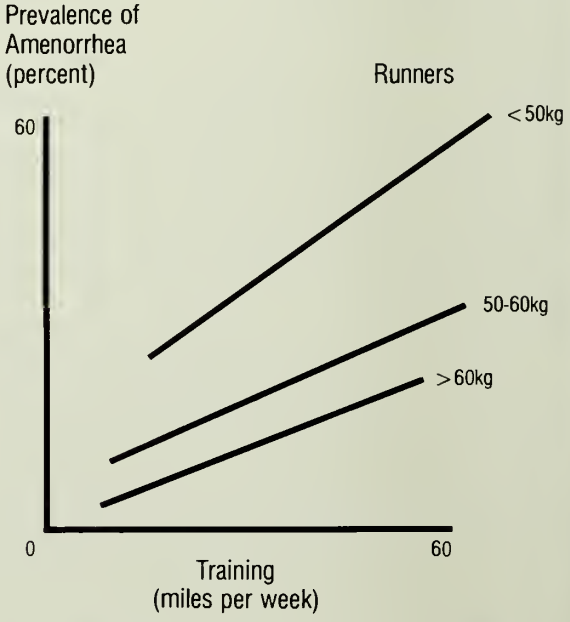

Figure 3.—Relationship of amenorrhea and weekly training mileage. Runners were grouped into three categories of body weight (from Sanborn et al,[24] with permission of authors and publisher).

menses before training remained regular and that the pretraining menstrual pattern was the best predictor of menstrual function during training.[26]

Parity is another factor involved. Dale and co-workers found that 51% of nulliparous runners were amenorrheic, while the prevalence was only 21% in multiparous runners.[21] Stress and nutrition are also factors implicated in menstrual dysfunction. Schwartz and colleagues showed a lower protein intake and a higher subjective stress level in runners who had amenorrhea compared with normal menstruating runners and normal controls.[36] However, there were no differences in standard psychological profiles between runners and controls.

Hormonal Changes Found in Female Athletes

Gonadotropins. In evaluating the effect of sports on menstrual function, it is important to examine the effects of exercise on various pituitary and ovarian hormones. Numerous studies have examined the effects of exercise on gonadotropins (see Table 3).[21,22,37,45-50] "Acute exercise"—that is, the short-term effects of an intense level of exercise—tends to cause no change or a brief increase in gonadotropin secretion.[45,46] Demers and associates, however, found decreased levels of LH and FSH with exercise.[48] Most studies show no gonadotropin changes in ovulatory runners and decreased levels in runners with amenorrhea.[21,22,49] However, Schwartz and co-workers found elevated LH levels in amenorrheic runners[37] and Bonen and colleagues found elevated LH levels and short luteal phases in swimmers.[50]

Steroid hormones. Serum estradiol and progesterone levels are increased with acute exercise (Table 4).[45] The effects of long-term exercise, however, especially in amenorrheic runners, seems to be the reverse.[21,22,47,50,51] Dale and associates took weekly blood specimens from 14 runners. Based on serum progesterone levels, 50% were ovulatory and had cyclic estrogen and progesterone levels.[21] Both estrogen and progesterone levels were low in runners who had amenorrhea.

Fat tissue cells are an extragonadal site of estrogen production due to aromatization of androgens to estrogens. It is possible that with less fat tissue, there is a decrease in estrogen and a resultant decrease in pituitary sensitivity to GnRH, leading to less ovarian stimulation.[35] Levels of 2-hydroxyestrone (a very weak estrogen) have been reported to be increased in thin women.[52,53] This could lead to either decreases in LH production[54] or understimulation of the endometrium.[52]

Prolactin. The prolactin level rises sharply with exercise

TABLE 3.—*Effect of Exercise on Gonadotropins*

Study	Population	Number	Hormones	
			LH	FSH
Jurkowski et al, 1978[45]	Runners (acute exercise)*	9	No change	Increased
Shangold et al, 1979[46]	Runners (chronic exercise)*	1	?Slight decrease in midcycle surge	No change
Dale et al, 1979[21]	Runners			
	Ovulatory	7	No change	No change
	Oligomenorrheic	7	Decreased	Decreased
Schwartz et al, 1980[37]	Runners			
	Ovulatory	12	No change	No change
	Amenorrheic	66	Increased	No change
Baker et al, 1981[22]	Runners			
	Amenorrheic	9	Decreased	No change
	Ovulatory	14	No change	No change
Demers et al, 1981[48]	Runners	24	Decreased	Decreased
McArthur et al, 1980[49]	Amenorrheic runners	3	Decreased	Normal
Bonen et al, 1981[50]	Swimmers	4	Elevated level and decreased time from LH surge to onset of menses in swimmers	Decreased compared with controls
	Teenaged controls	4		

FSH = follicle-stimulating hormone, LH = luteinizing hormone

*"Acute exercise" refers to the short-term effects of exercise; "chronic exercise" refers to the effects of a long-term, ongoing exercise level, such as in endurance training

TABLE 4.—*Effect of Exercise on Steroid Hormones*

Study	Population	Number	Steroid Hormone Levels	
			Estradiol	Progesterone
Jurkowski et al, 1978[45]	Acute exercise*	9	Increased	Increased
Shangold et al, 1979[46]	Chronic exercise*	1	No change	Decreased
Baker et al, 1981[22]	Amenorrheic runners	9	Lower in amenorrheic group	Not measured
	Regular cycles	14		
Dale et al, 1979[21]	Ovulatory runners	7	No change	No change
	Oligomenorrheic	7	Decreased	Decreased
Bonen et al, 1981[50]	Swimmers	4	Lower in swimmers	Lower in swimmers
	Teenaged controls	4		

*See Table 3 for explanation of "acute" and "chronic" exercise.

TABLE 5.—*Effect of Exercise on Prolactin*

Study	Population	Prolactin
Cohen et al, 1982[27]	Ballet dancers	0
Shangold et al, 1981[51]	Acute exercise*	Increased
Boyden et al, 1982[55]	Endurance training	↓Baseline, ↑responsiveness to TRH
Cumming et al, 1982[56]	Amenorrheic athletes	Decreased

TRH = thyrotropin-releasing hormone

*See Table 3 for explanation of "acute exercise"

(Table 5).[51] With endurance training, however, the baseline prolactin level decreases[55] and is decreased in amenorrheic athletes.[56] There is no evidence that strenuous exercise sustains a hyperprolactinemia and thus produces amenorrhea.[51]

Other hormones. Studies have shown normal levels of testosterone in female runners.[21,22,37,48,51] In several of these studies, testosterone levels were higher in athletes than in controls but still in the normal range.[21,48] Androstenedione levels have been reported to be normal.[21,37]

Reversibility and Prognosis

Evidence suggests that exercise-induced menstrual dysfunction is reversible. Stager and colleagues found that 83% of long-distance runners with amenorrhea had a return of normal menses within two months and none had amenorrhea six months after discontinuing training.[39] Normal reproductive function was found in swimmers in a ten-year follow-up after training stopped.[57] Finally, amenorrhea resolves in rowers[58] and ballet dancers after the close of a season.[30,33,34,41] The prognosis in regards to fertility is good.[20] Moreover, athletes have shorter labors and fewer obstetric complications.[58] No evidence exists that early training leads to permanent menstrual dysfunction.

One potential problem for athletes is that of hypoestrogenization and premature bone loss. Cann and co-workers studied 36 women with amenorrhea and 50 controls.[59] Of the amenorrheic women, ten had amenorrhea due to athletic activities. This group averaged 76% of the control group's vertebral mineral content as measured by computed tomographic scans. Drinkwater and associates compared regional bone mass in 14 runners who had amenorrhea with 14 matched peers who had normal menses.[60] The vertebral bone mass was significantly lower in the amenorrheic runners. No differences were detected in radial bone mass. Amenorrheic runners had lower mean estradiol levels and progesterone peaks. Lindberg and colleagues compared bone density in 11 runners with amenorrhea, 5 runners with oligomenorrhea, 15 runners with normal menses and menstrual cycles, 14 eumenorrheic nonrunners and 10 postmenopausal women.[61] Mineral content was measured using both a single-photon absorptiometer and the more sensitive dual-photon absorptiometer. Peripheral bone mineral content and spinal bone mineral content were lower in runners with amenorrhea than in normal controls and eumenorrheic runners. It is possible that the bone loss in these studies is induced by a hypoestrogen state due to hypothalamic pituitary dysfunction. The clinical significance of these studies needs to be assessed.

Effect of Menses on Athletes

The effect of menstruation on athletic performance also deserves attention. No variation in skill, speed or accuracy measurements were associated with the menstrual cycle in normal women and the measured outcome was similar in four performance tests during four phases of menses.[62] Stephenson and co-workers found the anaerobic threshold, work capacity and perceived exertion unchanged throughout the menstrual cycle.[63] On the other hand, Doring[64] found a decrease in coordination during and before menses and Doskin and associates[65] found a decrease in exercise tolerance during the premenstrual phase. Even with the possibility of a slight drop in performance during or just before menstruation, however, there is no reason for women to avoid athletic participation during this time.

Summary

Menstrual dysfunction due to athletic participation appears to be a real phenomenon and may be related to training schedule and intensity, age at onset of training, stress, body composition and weight loss. However, athletes with amenorrhea deserve the same evaluation as nonathletes for secondary causes, such as pregnancy, prolactinoma and ovarian and hypothalamic pituitary failure. Athletic-induced menstrual disorders appear reversible with no loss of reproductive capacity. The question of osteoporosis in amenorrheic athletes and the role of estrogen replacement needs further evaluation and investigation.

Weight Change and Menstrual Dysfunction

The incidence of eating disorders, especially anorexia nervosa and bulimia, has increased substantially in America and Europe during the past 10 to 15 years.[66] In fact, the number experiencing this syndrome in some fashion may have reached epidemic proportions. In addition, dieting is common in mildly to greatly obese patients. Evidence supports a correlation between weight loss and amenorrhea. Holmberg and Nylander studied 54 consecutive patients with amenorrhea—51 patients were discovered to have weight loss as a cause, of which 41 were diagnosed as having anorexia nervosa.[67] Knuth and co-workers found amenorrhea secondary to loss of weight in 39 of 170 consecutively investigated patients with amenorrhea.[68] Graham and colleagues studied four obese patients voluntarily losing weight.[69] Each lost 18 to 23 kg (40 to 50 lb) and in all four hypoestrogenemia and amenorrhea developed with the weight loss. Wentz found a 15% or more loss of body weight associated with secondary amenorrhea.[70]

Weight Loss and Gonadotropins

Gonadotropins and GnRH are affected by weight loss. A low FSH or LH level is found in many patients with simple weight loss or anorexia nervosa.[71-73] The secretion of LH in patients with anorexia nervosa or severe weight loss often regresses to a prepubertal pattern.[74] In addition, the response of LH to GnRH is often blunted[72,75,76] or delayed.[73,77] This suggests hypothalamic pituitary dysfunction in women with pronounced weight loss.

The alteration of menses by weight loss may also be explained by the metabolism of androgens and estrogens by fat tissue. Androstenedione is converted to estrone and, to a lesser degree, estradiol in fat tissue.[78] Alterations in fat tissue and the consequent changes in estrogen and androgen metabolism may affect the hypothalamic pituitary feedback. Levels

of 2-hydroxyestrone, a relatively inactive metabolite of estradiol, may be elevated in patients with anorexia.[52]

There is also evidence against weight loss as a primary factor in amenorrhea. From 7% to 24% of women with anorexia nervosa become amenorrheic before any weight loss.[79] In addition, 13% to 50% of anorexic women continue to have amenorrhea despite attaining their ideal body weight.[80]

Drug Use and Menstrual Dysfunction

Drug use, although leveling off in recent years, is common among American youth and young adults. About 1 in every 16 high school seniors smokes marijuana on a daily basis.[2] The same number drink alcohol on a daily basis.[2] Many other drugs including cocaine, heroin, hallucinogens, sedatives and amphetamines are abused but to a lesser degree. About 100,000 heroin-dependent women in the United States are in the childbearing age.[81]

A high prevalence of menstrual dysfunction has been reported with narcotic use. Stoffer studied 100 female patients at the Lexington Research Center.[82] Of 81 heroin addicts, 6 (7%) had menstrual dysfunction before drug use, 73 (90%) during and 39 (48%) after drug abuse. Infertility was found in 16% of drug users before drug abuse, 63% during and 6% after. Gaulden and colleagues[3] interviewed 74 heroin addicts and found menstrual abnormalities in 2 (3%) before drug use, 47 (64%) during drug use and 7 (10%) after drug use was stopped. Santen and co-workers found menstrual abnormalities in 5% of women before drug use, 70% during heroin use and 70% during methadone use.[83]

From studies of morphine in animals, it is likely that heroin and methadone alter ovulatory mechanisms by interfering with hypothalamic function.[83] Few studies are available, however, on the exact mechanisms in humans. Gaulden and associates studied hypothalamic function in women with heroin or methadone addiction.[3] Those with seemingly anovulatory cycles had abnormal LH and FSH release with no midcycle peaks and no positive feedback with large doses of estradiol. Tetrahydrocannabinol may also inhibit gonadotropins.[84] In rats, the LH surge can be inhibited by injecting tetrahydrocannabinol.[85] However, doses used in this study were higher than normally ingested doses in humans.

Licit drugs have been reported to cause amenorrhea and galactorrhea including phenothiazines, benzodiazepines and isoniazid.[86] Drug use and abuse should be evaluated carefully when evaluating women with menstrual abnormalities.

Menstrual Dysfunction and Chronic Illnesses

With ever-improving medical technology, the number of patients surviving with chronic illness continues to rise. Many of these illnesses, such as chronic renal failure, cystic fibrosis, cancer and inflammatory bowel disease, can have a pronounced impact on menstrual function.

Women with chronic renal failure can have significant menstrual abnormalities. Rice studied 24 patients with chronic renal failure.[87] Hypomenorrhea developed in 22 of the group, progressing to amenorrhea in 18 during the predialysis phase. After hemodialysis, 15 patients returned to having normal menses with 10 noting heavier periods and 9 increased frequency of menses; 11 patients required gynecologic consultation for dysfunctional uterine bleeding. Merkatz and co-workers studied menstrual patterns and fertility in 27 renal transplant patients.[88] Amenorrhea was present in 26 of the women before transplant. Recovery of menses following transplant correlated with clinical grades. Of 17 of the women with excellent clinical grades, 12 had regular menses compared with 1 of 5 with good clinical grades and 0 of 5 with fair or poor clinical grades. The typical pattern observed in women with chronic renal failure is hypomenorrhea or amenorrhea while azotemic.[87] Return of menses occurs in many while receiving hemodialysis, with an approximate 50% prevalence of hypermenorrhea. After renal transplantation, many return to regular ovulatory cycles with pregnancies reported.[87]

Lim and associates examined the hypothalamic-pituitary axis in women with chronic renal failure.[89] Eight of nine patients had low or normal LH and FSH levels, whereas these levels were elevated in one of nine patients. Estradiol was low in seven of nine and normal in two of nine. Progesterone was undetectable in seven patients and low in two. Eight of nine patients had elevated prolactin levels, with five complaining of galactorrhea. Cyclic changes in LH and FSH levels were not detected. A loss of positive feedback of LH and FSH to estradiol was detected, suggesting a hypothalamic pituitary problem. Mooradian and Morley also reviewed endocrine dysfunction in chronic renal failure patients[90] and suggested that in addition to a hypothalamic pituitary defect, a primary ovarian defect exists. This is suggested by the elevated FSH levels in some patients and the failure of estrogen to rise in response to high gonadotropin levels after administration of clomiphene. The suppression of hyperprolactinemia by bromocriptine in these women, with a resumption of menses in one patient, suggests that hyperprolactinemia may cause amenorrhea in some uremic patients.[91]

Several menstrual abnormalities were noted in a review of female patients with cystic fibrosis.[4] Those patients who were menarchal had an approximate 1.5-year delay in menarche from the normal mean. In addition, 57% had either dysfunctional uterine bleeding or oligomenorrhea.

Ulcerative colitis and Crohn's disease are most common in the childbearing years. Fertility is only minimally, if at all, compromised,[92] suggesting that unless malnutrition is severe, menstrual disorders are not severe.

Stillman and associates have reviewed 208 children ages 0 to 17 years with various tumors,[93] 52% of whom received irradiation and 47% chemotherapy. Ovarian failure developed in 12%, and all of these had received irradiation. Ovarian failure did not develop in any woman who had at least one ovary outside the treatment field. Chemotherapy also has the potential of destroying ovarian premordial follicles, leading to amenorrhea and infertility. This has been reported not only in oncology patients but in rheumatology and nephrology patients receiving these drugs.[94] The alkylating agents including cyclophosphamide, chlorambucil and melphalan as well as combination chemotherapy[95,96] appear to do the most damage. A report of female patients receiving MOPP (mechlorethamine, Oncovin [vincristine], procarbazine and prednisone) combination chemotherapy showed that 8 of 14 became amenorrheic associated with elevated FSH levels.[96] Chemotherapy does less damage to prepubertal ovaries due to their quiescent state.[93,95,97]

Finally, menstrual disorders, primarily dysfunctional uterine bleeding, are commonly associated with those persons who have clotting or platelet abnormalities.

Menstrual Disorders in Miscellaneous Conditions

Stress

The prevalence of menstrual dysfunction among college students has been reported to be from 13.9% to 21%.[98,99] McCormick found a 20% prevalence of oligomenorrhea and a 2.8% prevalence of secondary amenorrhea among nursing students.[100] In a retrospective evaluation of the epidemiology of secondary amenorrhea, psychological stress was reported in 34.4% of amenorrheic women versus 11.5% of control women.[101] Yaginuma[102] noted that in 32 patients with stress amenorrhea of less than one year's duration, FSH and LH levels and responsiveness to GnRH were normal. In 11 of 14 patients with stress amenorrhea longer than one year, however, FSH and LH levels were high, with an exaggerated release responsiveness to GnRH.

Flying

Airline stewardesses have an increased prevalence (18% to 28%) of menstrual irregularities.[103-105] This seems to resolve with time. The abnormalities are worse with jet flying, especially intercontinental flights. No evidence of increased infertility exists after discontinuing flying.

Role of β-Endorphins

β-Endorphins are oligopeptides with morphinelike activity.[79] The greatest concentration of β-endorphins is in the region of the arcuate nucleus and the medial eminence of the hypothalamus.[106] Large concentrations are also present in the preoptic-anterior hypothalamic regions of the brain, which is one of the regulatory centers of cyclic regulation of LH release.[106]

Endorphins seem to have a cyclic release similar to the menstrual cycle and may be involved in modulating gonadotropin release. Evidence in rats suggests that β-endorphins may inhibit the LH surge, whereas administering naloxone, an opiate antagonist, may lead to an LH surge.[6,9,106-109] Wehrenberg and colleagues found mean β-endorphin levels in the hypophyseal portal blood of rhesus monkeys of 737 pg per ml during the follicular phase, 1,678 pg per ml during the luteal phase and undetectable levels during menstruation.[107] Vrbicky and co-workers studied β-endorphin levels and LH, estradiol and progesterone levels in 26 cycles of 15 women. A β-endorphin spike occurred before the estradiol and LH surge.[79]

Many of the conditions discussed in this paper can affect β-endorphin levels. Exercise has been associated with elevated β-endorphin levels.[110-113] Patients with anorexia nervosa have had elevated β-endorphins at their minimum weight.[114] Patients with uremia have had greatly elevated serum β-endorphin levels compared with controls.[115] Patients with rheumatoid arthritis and lupus have had decreased levels of circulating β-endorphins.[116] Stress has been associated with elevated β-endorphin levels.[117] Last, women with heroin addiction obviously have elevated activity of circulating compounds with opiate activity from exogenous opioids. Thus, the alteration of β-endorphin levels in these conditions may affect ovulation and menstrual cycles through their effect on the hypothalamus.

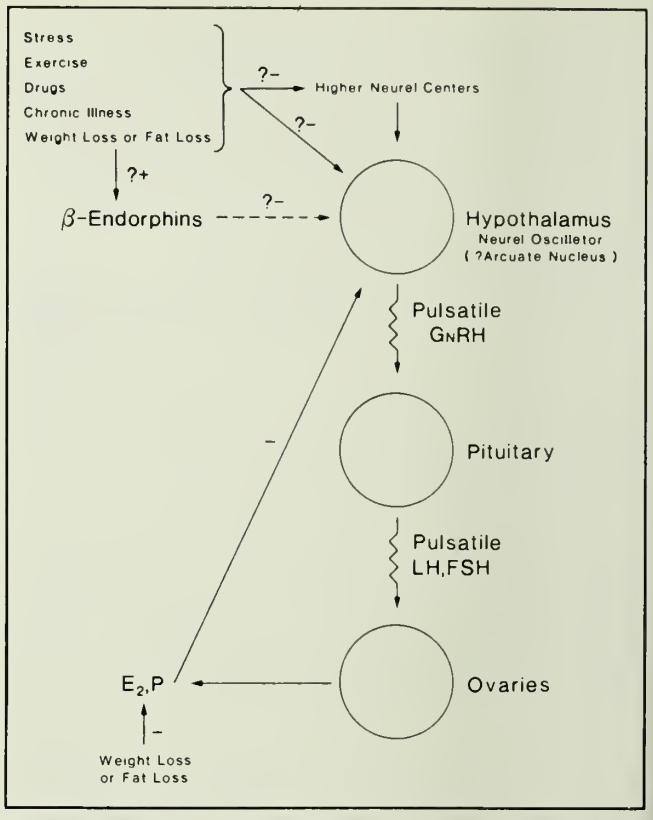

Figure 4.—Model of the roles of pathophysiologic stress, exercise, drugs, chronic illness and weight loss in inducing amenorrhea. Pathophysiologic states may act through higher neural centers, β-endorphins or directly on the hypothalamus to alter pulsatile release of gonadotropin-releasing hormone (GnRH), resulting in altered luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, altered estrogen secretion and amenorrhea. Alternatively, weight loss may alter estrogen metabolism with resultant negative feedback on hypothalamus or resulting in less estrogen to stimulate the endometrium. E_2, P = estradiol, progesterone

In summary, there are multiple levels where the pathophysiologic states discussed in this article could affect the menstrual cycle (Figure 4). Stress, exercise, drugs and chronic illnesses may affect the pulsatile release of GnRH through β-endorphins or by direct action on the hypothalamus. Weight loss through associated changes in estrogen metabolism may alter the hypothalamic-pituitary axis. At present, the most serious quesion and concern is the presence and degree of osteoporosis in athletes and other women with amenorrhea and whether estrogen replacement is advisable in these women.

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Medical Progress

Prostaglandins, Thromboxanes and Leukotrienes in Clinical Medicine

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Although prostaglandin research began about 50 years ago, many of the most important advances in understanding the biochemistry, physiology and pharmacology have taken place within the past five to ten years. There is great potential for the extension of this research to the clinical practice of medicine. At this time, the most common interaction that clinicians have with the prostaglandin field is in administering nonsteroidal anti-inflammatory drugs, which function by inhibiting prostaglandins. The uses of these drugs include treating not only inflammation, but also dysmenorrhea, some renal diseases, thrombotic diseases and some metabolic disorders. Prostaglandin analogs, with their potent effects on uterine contraction, are in common use in obstetrics. Other analogs with gastric and duodenal cytoprotective effects are useful in treating peptic ulcer disease. Future benefits from prostaglandin and leukotriene research may include new therapy for inflammatory and hypersensitivity diseases such as asthma, inflammatory bowel disease and dermatitis.

(Zipser RD, Laffi G: Prostaglandins, thromboxanes and leukotrienes in clinical medicine [Medical Progress]. West J Med 1985 Oct; 143:485-497)

In this review we emphasize those areas of prostaglandin, thromboxane and leukotriene (collectively called "eicosanoids") biochemistry and physiology that interact with the contemporary practice of medicine. Additional emphasis will include discussions of assay methods, inhibitors and pharmacology to assist readers in interpreting the increasing number of publications that cover these areas. Eicosanoid research has made important contributions to several subspecialties, including cardiovascular and thrombotic disease, immunity and inflammation, reproduction, nephrology, pulmonary disease, gastroenterology and metabolic disorders. These areas will be discussed in more detail.

History and Introduction

The history of prostaglandins began in the 1930s with the observation by two New York gynecologists, Kurzrok and Lieb, that human semen caused contractions and relaxation of human myometrium.[1] These observations were soon confirmed by Goldblatt in England[2] and by von Euler in Sweden.[3] In 1935 von Euler purified the active compounds by acid lipid extraction of sheep vesicular glands and coined the term "prostaglandin" in the belief that the prostate was the source.[4] At about the same time, the history of leukotrienes began with the finding by Feldberg, Kellaway and Trethewie of a factor from dog lung exposed to cobra venom and a similar factor from sensitized guinea pig lung that caused a slow, prolonged contraction of the guinea pig jejunum.[5,6] These factors were called slow-reacting substance of anaphylaxis (SRS-A) and later identified as a possible mediator of asthma and other hypersensitivity reactions. There was then a delay in progress until the 1960s when a series of major advances began in Sweden by Bergström and colleagues, including Samuelsson, and in The Netherlands by Van Dorp. Prostaglandins were identified as a group of compounds rather than a single substance, and arachidonic acid was identified as their precursor.[7,8] Isolation of large amounts of natural prostaglandins from the Caribbean coral *Plexaura homomalla*, new methods of synthesis pioneered by Corey and others and extensive distribution of these products to investigators by the Upjohn Company and other pharmaceutical companies permitted intensive widespread study of these compounds. It was soon recognized that prostaglandins were produced by nearly all biologic tissue. Profound pharmacologic effects of these compounds were shown on smooth muscle contraction, cell secretions and platelet aggregation, which fostered the concept that prostaglandins functioned as local mediators of many biologic systems.

In 1971 the number of publications in this field began to

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ABBREVIATIONS USED IN TEXT

cyclic AMP = adenosine 3′:5′-cyclic phosphate
HETE = hydroxyeicosatetraenoic acid
HPETE = hydroperoxyeicosatetraenoic acid
LT = leukotriene
NSAID = nonsteroidal anti-inflammatory drug
PG = prostaglandin
SRS-A = slow-reacting substance of anaphylaxis
Tx = thromboxane

explode with the key discovery by Vane and colleagues in England that aspirin, indomethacin and other nonsteroidal anti-inflammatory drugs inhibited prostaglandin biosynthesis.[9] Over the past 12 years there have been more than 26,000 publications. Major highlights included the 1975 report by Hamberg, Svensson and Samuelsson identifying the potent platelet-aggregatory substance, thromboxane A_2,[10] and the 1976 identification by Moncada, Vane and co-workers of the antiaggregatory vasodilator, prostaglandin I_2.[11] During this time, parallel progress was made in studies of SRS-A including identification of arachidonic acid as the precursor.[12] In 1979 the Samuelsson laboratory announced the structures of the leukotrienes that make up the compounds of SRS-A.[13,14] New enzymatic pathways of arachidonic acid metabolism involving the lipoxygenase pathway were identified, as well as potent new biologic mediators of inflammation. In 1982 the Nobel prize for physiology and medicine was awarded to Sune Bergström, Bengt Samuelsson and John Vane for their major contributions to this field. The field continues to expand with an escalating number of publications on new metabolites of arachidonic acid, new inhibitors and a plethora of data on prostaglandin involvement in physiology.

Biochemistry

Prostaglandins and thromboxanes are derived from 20-carbon fatty acids. In mammals, arachidonic acid is the major precursor of prostaglandins ("2" series prostaglandins) and is localized primarily in the membrane phospholipids. Dihomo-γ-linolenic acid is the precursor of the "1" series prostaglandins (present only in trace amounts), and eicosapentaenoic acid (predominant in fish oils) is converted to some extent to the "3" series prostaglandins (Figure 1). Extreme variations in dietary fat and eicosapentaenoic acid, such as that derived from the marine diet of Greenland Eskimos, can compete with the enzymes governing arachidonic acid metabolism and alter prostaglandin and thromboxane synthesis, resulting in biologic changes such as prolonged bleeding time.[15] In essential fatty acid deficiency, prostaglandin synthesis is diminished, which may account for some of the clinical manifestations such as dermopathy.

The cascade of prostaglandin synthesis begins with the release of arachidonic acid from phospholipids via activation of phospholipase (primarily phospholipase A_2). This rate-limiting step is initiated by hormonal, ischemic, neural, inflammatory or other stimuli varying from cell to cell. Once released, arachidonic acid is available for enzymatic oxidation into hydroperoxy and hydroxy derivatives. For example, the 12-lipoxygenase enzyme in platelets induces formation of the unstable 12-hydroperoxyeicosatetraenoic acid (12-HPETE), which is reduced by peroxidase to the stable 12-hydroxyeicosatetraenoic acid (12-HETE), with unclear bio-

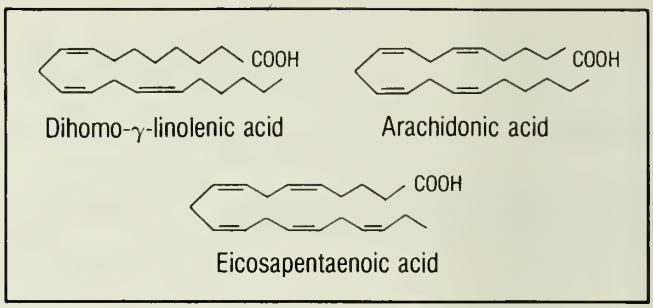

Figure 1.—Fatty acid precursors of eicosanoids.

logic activity. By a similar mechanism, 15-lipoxygenase in leukocytes forms 15-HPETE and 15-HETE, which may have some inflammatory activity. Two other enzymatic oxidation sites at carbon 11 and 5 are of more biologic importance, leading to formation of prostaglandins and leukotrienes, respectively. Aside from the biologic activity of the arachidonic acid metabolites, the oxidation-peroxidation reactions may have more direct biologic effects by forming oxygen radicals, which may induce tissue injury and carcinogenesis.[16,17]

Oxidation in the microsomes of most mammalian cells by the cyclooxygenase enzyme (originally called prostaglandin synthetase) at C 11 induces formation of a cyclopentane ring and a cyclic endoperoxide (prostaglandin [PG] G_2) (Figure 2). PGG_2 is rapidly converted by peroxidase activity to PGH_2, the unstable common intermediate of prostaglandins and thromboxanes. Conversion of PGH_2 to thromboxanes or to various prostaglandins is effected by enzyme systems characteristic for each specific cell type. Several examples are listed. PGE_2 and $PGF_{2\alpha}$ are the classic prostaglandins present in many tissues, including the kidney and uterus, with diverse possible physiologic actions including smooth muscle contraction, pyretic reactions and inflammatory interactions. PGI_2 (prostacyclin) is particularly prominent in vascular endothelium and possesses both vasodilatory and antiaggregatory actions. PGD_2 is a major product of mast cells and brain tissue. Thromboxane A_2 production is most commonly associated with platelet aggregation and vasoconstriction (see reviews.)[18-20]

Leukotriene formation, which predominates in polynuclear leukocytes and some mononuclear cells, results from 5-lipoxygenase activity forming 5-HPETE and conversion to an epoxide moiety, the unstable common intermediate, leukotriene (LT) A_4. LTA_4 can then react with water to form the potent chemokinetic and chemotactic leukotriene, LTB_4. Alternatively, LTA_4 reacting with glutathione leads to the peptide derivatives, LTC_4, LTD_4 and LTE_4, which make up the potent inflammatory mediators collectively known as SRS-A (see reviews.)[12,21-24] Recently, new compounds and pathways have been proposed, such as metabolites of 15-lipoxygenase, called lipoxins that may also have inflammatory functions.[25]

Eicosanoid Inhibitors

By far the most common interaction that clinicians have with the field of prostaglandins is the therapeutic use of nonsteroidal anti-inflammatory drugs (NSAIDs) and of corticosteroids for inflammatory conditions. The use of anti-inflammatory agents, however, certainly preceded prostaglandin research (willow bark has been used for centuries,

for instance, and acetylsalicylic acid has been commercially available since about 1900), and it is not established that all the effects of these drugs can be explained by their inhibiting the cyclooxygenase enzyme. A detailed review of NSAID pharmacology and clinical experience exceeds the scope of this summary, and excellent reviews are available.[26-32] Instead, in this summary we will briefly consider the modes of action of these agents, the prospect for more specific inhibitors and the relevance of the effects of these agents to our understanding of prostaglandin physiology.

In general, NSAIDs function by inhibiting the cyclooxygenase enzyme, thereby diminishing the conversion of arachidonic acid to PGH_2 and to other prostaglandins and thromboxanes.[9,13] The anti-inflammatory, analgesic and antipyretic actions of aspirinlike drugs are attributed to inhibition of prostaglandins, particularly PGE_2. Other anti-inflammatory drugs such as colchicine and gold do not inhibit prostaglandin. The NSAID effects on cyclooxygenase include diminished peroxidase activity and reduced generation of oxygen radicals, which may also reduce tissue damage and possibly reduce the formation of carcinogens. The anti-inflammatory potency of NSAIDs generally parallels the prostaglandin-inhibiting potency, although there is some variation in different tissues. For example, compared with newer NSAIDs, aspirin is a relatively weak prostaglandin inhibitor, but it causes a more prolonged inhibition of platelet thromboxane because the irreversibly acetylated cyclooxygenase enzyme cannot be regenerated in the life span of these cells. Acetaminophen is a poor cyclooxygenase inhibitor in most in vitro systems, but there is evidence that it may be effective in brain tissue, explaining its antipyretic and analgesic effects without peripheral anti-inflammatory effects.[32] Compared with indomethacin and ibuprofen, the new NSAID sulindac is less likely to cause acute renal impairment in patients with chronic glomerulonephritis or in those with cirrhosis and ascites[33,34]; however, it is not clear if this apparent renal sparing of sulindac is the result of rapid inactivation of the drug by the kidney or of overall weaker cyclooxygenase activity. Sodium salicylate reduces prostaglandin synthesis in sites of inflammation and in the pancreatic islet without inhibiting gastric mucosal or platelet prostaglandins.[35]

Finally, caution is urged in extrapolating specific physiologic functions of prostaglandins from the effects of NSAIDs. The NSAIDs are considered "nonspecific" because they inhibit all of the cyclooxygenase products and also because they act on multiple organ systems. The observed effects may be the culmination of effects on several biologic systems. These agents also have nonprostaglandin effects. For example, indo-

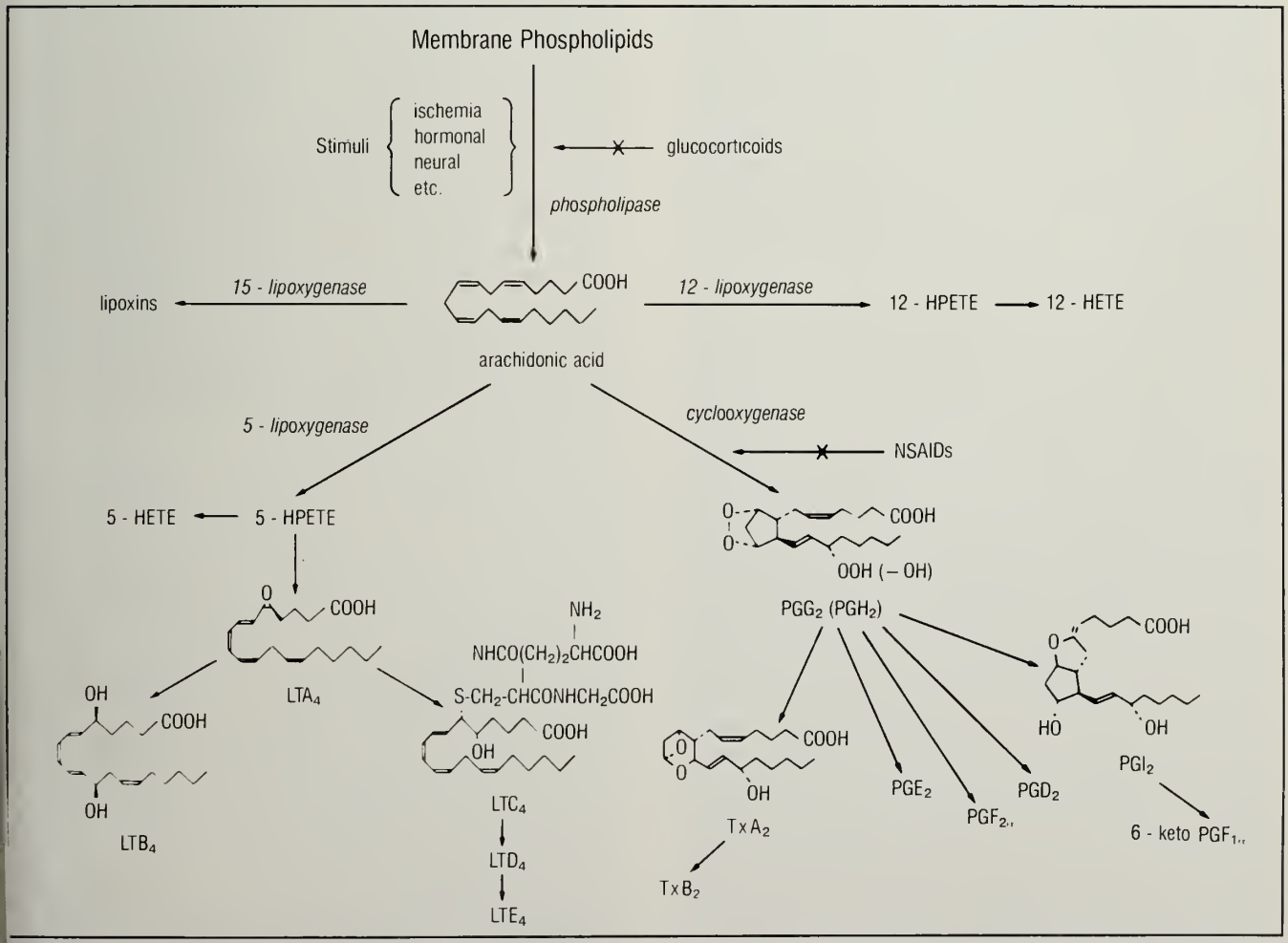

Figure 2.—Eicosanoid biochemical pathways. HETE = hydroxyeicosatetraenoic acid; HPETE = hydroperoxyeicosatetraenoic acid; LT (A_4, B_4, C_4, D_4, E_4) = leukotriene; NSAIDs = nonsteroidal anti-inflammatory drugs; PG (D_2, E_2, $F_{1\alpha}$, $F_{2\alpha}$, G_2, H_2, I_2) = prostaglandin; Tx(A_2, B_2) = thromboxane

methacin in high concentrations affects protein kinase, calcium flux and other enzymes.[29] In addition, at least some of the NSAIDs also block arachidonic acid metabolism by the 15-lipoxygenase enzyme, perhaps contributing to the anti-inflammatory effects.[30]

Inhibitors of specific enzyme pathways distal to the cyclooxygenase enzyme have recently been developed with possible clinical implications. The first to undergo clinical trials have been imidazole and pyridine derivatives, which selectively block thromboxane synthetase without reducing other cyclooxygenase products.[36,37] The premise is that these drugs will have antithrombotic action because they block platelet thromboxane without reducing blood vessel synthesis of prostacyclin. Early clinical trials of patients with thrombotic and vasospastic disease have suggested some benefit but no clear advantage over aspirin. Clinical application may have more promise in other disease states such as glomerulonephritis.[38]

Pharmacologic administration of glucocorticoids causes many effects unrelated to arachidonic acid metabolism. At least in some biologic systems, these steroids inhibit the release of arachidonic acid from membrane phospholipids.[39] This effect involves synthesis of a glycoprotein that inhibits phospholipase A_2 activity.[40,41] The new term "lipocortins" best describes this family of compounds.[42] In susceptible tissue, all arachidonic acid metabolites are inhibited, including cyclooxygenase and lipoxygenase systems. The anticipated reduction in leukotriene synthesis is the popular explanation for some of the glucocorticoid efficacy in cases of hypersensitivity reaction such as asthma and in inflammatory states. Fostered by these studies and the increasing amount of data on the potent effects of leukotrienes, there is currently an intense effort to develop specific leukotriene inhibitors for clinical uses that may include patients with asthma, inflammatory arthritis, dermatitis and inflammatory bowel disease.[43]

Methodologic Constraints

It has been the unfortunate recurring history of prostaglandin assays in clinical research that the early studies of each eicosanoid report biologic levels that greatly exceed those subsequently determined with better methods. The physiologic roles equated with the early measurements are then subsequently disproved. For example, many early studies of plasma and serum PGE_1, PGE_2, PGA_1 and PGA_2 reported normal values ranging from several hundred picograms to several hundred nanograms per milliliter. Theories on the pathogenesis of blood pressure regulation, sodium balance and diarrheal states were widely promulgated based on these reports. Later studies using mass spectrometry confirmed that PGA_1 and PGA_2 did not exist in detectable amounts in human circulation and that PGE_2 plasma levels were less than 30 pg per ml. Similar misadventures have occurred with reports of circulating levels of prostacyclin (PGI_2), thromboxane B_2, $PGF_{2\alpha}$ and some prostaglandin metabolites (see reviews).[19,44,45] It is now clear that none of these compounds are present in sufficient concentration to act as circulating hormones; instead, eicosanoids function primarily as local mediators. The methodologic problems are caused by several factors, which include poor antiserum specificity in early radioimmunoassays, the myriad of unidentified prostaglandin metabolites that may cross-react in these assays, poor specificity and sensitivity of bioassays, the pronounced potential for artifactual generation of eicosanoids during sample collection—such as from platelet release and vessel wall trauma during blood sampling—the short biologic and chemical half-life of many eicosanoids and unidentified interfering substances in early mass spectrometry. It behooves the reader of prostaglandin research to be cautious of all reports of circulating blood and urine levels unless extensive validating studies (particularly comparison with mass spectrometry) have been presented. Measurements of tissue concentration of eicosanoids are suspect because these compounds are generally not stored and because they are readily produced by tissue trauma, such as by biopsy. One technique to avoid these problems is to measure stable metabolites. For example, urinary excretion of 2,3-dinor-$PGF_{1\alpha}$ and 2,3-dinor-thromboxane B_2 appear to quantitatively reflect systemic production of prostacyclin and thromboxane, respectively,[46] and plasma assay of a tetranor metabolite of $PGF_{2\alpha}$, which has a long half-life in circulation, accurately reflects systemic production of $PGF_{2\alpha}$.[47]

Cardiovascular and Thrombotic Diseases

The role of prostaglandins in controlling blood pressure has been a topic of dispute for almost 20 years since the isolation of prostaglandin A_2 from kidney medulla and the early reports claiming that circulating levels of PGA_2 were of sufficient concentration to affect blood pressure.[48-50] Later studies showed that PGA_2 was not present in the circulation.[51] Similarly, other vasodepressor prostaglandins such as PGI_2 exist in blood in concentrations too low to have circulating hormonal effects.[52] Nevertheless, it is likely that local vascular production of vasodilatory prostaglandins and possibly vasoconstrictor thromboxanes do function to modulate local vascular resistance, especially in response to vasopressor hormones and to volume. Thus, administering NSAIDs may increase blood pressure (aside from the sodium-retaining effects) in a few patients such as those with mineralocorticoid-induced hypertension,[53] and NSAIDs may blunt the effects of antihypertensive drugs.[54] The hemodynamic effects of these agents are particularly evident in patients with congestive heart failure.[55]

A more contemporary issue is the possible role of prostacyclin (PGI_2) and thromboxane (Tx) A_2 in regulating platelet aggregation in patients with thrombotic and atherosclerotic disease. Thromboxane A_2, a major arachidonic acid product of platelets, is a potent vasoconstrictor (similar in potency to angiotensin II), platelet-aggregatory stimulus (independent of adenosine diphosphate and thrombin) and bronchoconstrictor.[10] TxA_2 has a short half-life (30 seconds in aqueous media) and spontaneously converts to the inactive TxB_2. Following vascular wall trauma, collagen and other factors stimulate platelet aggregation and thromboxane release. Aspirin, other NSAIDs and selective thromboxane-synthesis inhibitors block thromboxane generation and prolong bleeding time in vivo and platelet aggregation in vitro.[9,56-58] Opposing effects result from PGI_2, the predominant arachidonic acid metabolite of intact vascular endothelium with vasodilatory and bronchodilatory properties.[11] PGI_2 inhibits platelet aggregation and prevents TxA_2 production via a platelet adenosine 3′:5′-cyclic phosphate (cyclic AMP)-mediated pathway.[57,59] Dipyridamole, an inhibitor of phosphodiesterase, also increases cyclic-AMP levels, inhibits platelet aggregation by cyclic

AMP of other mechanisms and potentiates the antiaggregatory effect of aspirin.[60] As with TxA_2, PGI_2, has a short half-life (about 1.5 minutes in aqueous solution), and it is converted to an inactive metabolite, 6-keto-prostaglandin $F_{1\alpha}$, but possibly also to an active metabolite, 6-keto-PGE_1, in some tissues. The general interpretation of these studies is that the intact endothelium prevents platelet adherence and aggregation via local generation of PGI_2 (plus several other antiplatelet factors). With disruption of the endothelium, initial platelet adherence occurs and platelet TxA_2 is then produced that causes local vasoconstriction and augments platelet aggregation at the injury site. Production of PGI_2 from normal endothelium adjacent to the injury site may be increased by the use of endoperoxide precursors (PGH_2) released during arachidonic acid metabolism from the platelets and taken up by the endothelium, thus preventing spread of platelet aggregation to normal endothelium (Figure 3).[57,59-61]

One clinical implication of these opposing effects of TxA_2 and PGI_2 is the concept that an imbalance of these products may contribute to thrombotic, atherosclerotic and vasospastic disease.[62] This concept is supported by several in vitro studies showing increased thromboxane generation from disease states susceptible to atherosclerosis, such as hypercholesterolemia[63] and diabetes mellitus.[64] Conversely, high-density lipoproteins are associated with a reduced risk of cardiovascular disease and in vitro studies have shown an increased endothelial PGI_2 response to high-density lipoprotein.[65] In addition, smoking decreases the urinary excretion of a PGI_2 metabolite.[66] Although the theories of imbalances of arachidonic acid metabolites as a cause of atherosclerosis are intriguing, rigorous evidence of clinical relevance is still lacking. Indeed, recent data suggest that systemic PGI_2 production may actually be increased rather than decreased in patients with atherosclerosis.[67] Based on this imbalance theory, therapeutic strategies to prevent cardiovascular disease that attempt to selectively reduce TxA_2 without impairing PGI_2 have been proposed, including administering very low doses of aspirin (to block platelet but not vascular cyclooxygenase), administering selective inhibitors of thromboxane synthetase and prescribing diets rich in eicosapentaenoic acid (fish oils).[68] Although controversy persists, increasing data suggest that administering aspirin (with or without dipyridamole) is of benefit in reducing the risk of myocardial infarction in some patients and in reducing reocclusion of saphenous vein coronary artery bypass grafts.[69-71] These data provide clinical support at least for the importance of platelet aggregation and thromboxane in these diseases. A role for PGI_2 is likely, but not proved.[72]

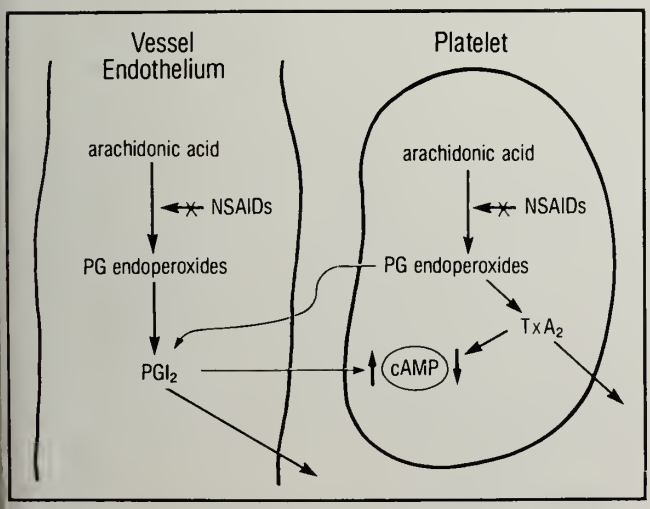

Figure 3.—Thromboxane (Tx) and prostacyclin (prostaglandin [PG]I_2) interactions from platelets and blood vessel endothelium. cAMP = cyclic AMP (adenosine 3′:5′-cyclic phosphate), NSAIDs = nonsteroidal anti-inflammatory drugs

Another exciting extension of prostaglandin research to cardiovascular disease is the pharmacologic administration of prostacyclin (PGI_2) or a stable analog for its platelet antiaggregatory and vasodilatory effects.[73] Prostacyclin has been substituted for heparin during extracorporeal circulation such as hemodialysis, cardiopulmonary bypass and charcoal perfusion.[74-77] Compared with the effects of heparin therapy, thrombocytopenia is reduced or prevented, most platelet functions are maintained and blood loss may also be reduced. The use of prostacyclin has also been advocated for treating patients who have atherosclerotic obstruction of extremities, central retinal vein occlusion, angina pectoris or ischemic strokes based on the premise that atherosclerotic arteries have decreased prostacyclin production. Initial results of uncontrolled studies are promising.[78,79] Earlier studies using infusions of PGE_1 also claimed relief of pain and ulcer healing in patients with chronic ischemia of the legs.[80] Open trials of prostacyclin infusion in patients with the Raynaud's phenomenon have also suggested prolonged improvement.[81] Results of double-blind controlled trials have suggested that these infusions are not consistently beneficial[82-84] and such therapy will probably not become clinically useful.

Immune and Inflammatory Responses

Perhaps the areas with the most rapidly expanding knowledge about eicosanoid physiology are those of immunity and inflammation.[21-23,28,31,85-88] Increased production of arachidonic acid metabolites occurs at sites of inflammation,[85-89] arising from the injured tissue, from inflammatory cells and from noninflammatory cells that are apparently stimulated by other products of inflammation.[90,91] Oxygen free radicals are generated by both cyclooxygenase and lipoxygenase pathways, and these products likely contribute to tissue injury.[92] Several prostaglandins, especially PGE_2, PGI_2 and possibly PGD_2, contribute to inflammation by increasing the blood flow (erythema), by dilating vessels and increasing capillary permeability (edema) and by increasing pain sensitivity to other mediators such as to bradykinin and histamine. Prostaglandins also have pyretic effects under some conditions such as following release of leukocytic pyrogen and endotoxin.[93,94] It is unclear whether the cyclooxygenase products have chemotactic and chemokinetic properties: discrepant results have been reported in several studies. However, leukotriene B_4 is a very potent chemotactic factor for neutrophils, eosinophils and mononuclear cells.[31,95] Some mono-HETEs are less potent chemotactic agents. LTB_4 also activates neutrophils by causing degranulation and superoxide generation. LTC_4, LTD_4 and LTE_4 (SRS-A) have vasoconstrictor activity; they also contribute to edema by increasing capillary permeability. These SRS-A factors are from 100-fold to 10,000-fold more potent than histamine in constricting pulmonary airways. It is apparent that the anti-inflammatory effects of NSAIDs and of corticosteroids function in part by inhibiting the eicosanoid

actions cited above. It should be emphasized that eicosanoids act primarily as potentiators (or in some cases as modulators), rather than as initiators, of inflammation. In some inflammatory conditions the effects of certain eicosanoids may predominate, favoring the use of specific blockers of the arachidonic acid cascade. For example, lipoxygenase products may be particularly important in cases of psoriasis,[96,97] inflammatory bowel disease[98] and rheumatoid arthritis,[99] whereas PGD_2 predominates in mastocytosis.[100]

In contrast to the apparent proinflammatory actions, eicosanoids generally suppress immune functions.[87,88] In low concentrations, PGE_2 suppresses T-lymphocyte functions that include antigenic stimulation, lymphokine production, lymphocyte migration, mitogen responsiveness and clonal proliferation. These actions are mediated by enhanced generation of cyclic AMP. LTB_4 and 15-HPETE may have similar effects. NK-cell and monocyte cytolytic activity is inhibited by PGE_2 and by lipoxins, although lipoxins may act independently of cyclic AMP. Prostaglandins may also inhibit B-cell function, either directly or via actions on other immune cells. Macrophages and monocytes produce large amounts of PGE_2 in response to lymphokines and other stimuli that include zymosan, endotoxins, antigen-antibody complexes and immunoglobulin-G fragments. A popular theory is that antigens stimulate lymphocyte production of lymphokines, which activate macrophages to produce prostaglandins. These prostaglandins then function to inhibit the lymphocyte function.[101] In cases of Hodgkin's disease the defect in cellular immunity is due to a population of prostaglandin-producing suppressor cells.[102] Immunosuppressive activity from macrophages (presumably via prostaglandin production) may contribute to the anergy present in patients with chronic inflammatory diseases such as Q fever, coccidioidomycosis and tuberculosis.[103]

These pieces of information are consistent with the theory that eicosanoids function predominantly as potentiators of acute inflammation, actions that are inhibited by corticosteroids and by NSAIDs. In contrast, in some chronic disease states, eicosanoids function to depress cellular immunity and prostaglandin inhibitors may act to stimulate cellular immune function.

Reproduction

Another important impact of prostaglandin research on clinical medicine involves reproduction, including the extensive use of exogenous prostaglandins as pharmacologic agents.[104-107]

Seminal fluid contains the highest concentration of prostaglandins of all human tissue, more than 100,000-fold more concentrated than in circulating plasma.[108,109] This observation has led to speculation that seminal fluid prostaglandins are involved in the contractile response of the vas deferens and the uterus, although the precise function in fertility is not established. There is some evidence, however, of diminished seminal fluid prostaglandin concentration in some infertile men who have no other apparent abnormality.[110]

There is pronounced species variation in the physiologic functions and pharmacologic effects of prostaglandins in female reproductive organs. In rats and rabbits, but not in humans, prostaglandins are obligatory mediators of ovulation.[111,112] Gonadotropin-stimulated cyclic AMP in the granulosa cell induces prostaglandin synthesis.[107,113] Indomethacin prevents follicular rupture, and exogenous prostaglandins reverse this effect. In many species including sheep, cows, horses and pigs, prostaglandin production (possibly $PGF_{2\alpha}$ from the uterus) is the key factor causing luteolysis.[113-115] Prostaglandin administration has been used to synchronize the estrous cycle of cows and other animals to facilitate artificial insemination.[116] In humans, there is no strong evidence that prostaglandins or prostaglandin inhibitors have direct effects on ovulation or on maintaining the corpus luteum. There is substantial evidence, however, that increased production of endometrial prostaglandins contributes to the symptoms of dysmenorrhea, and NSAIDs are now widely prescribed for these symptoms.[117-119] Several clinical trials have confirmed the safety and efficacy of these drugs for such symptoms as uterine cramps, headache, nausea and diarrhea.[120] NSAIDs are also used to treat dysfunctional uterine bleeding, especially in association with intrauterine contraceptive devices.[121,122]

During pregnancy, the uterus is particularly sensitive to PGE_2, $PGF_{2\alpha}$ and their analogs. Endogenous prostaglandins may mediate uterine contractions in nonsurgical abortions,[123] and exogenous prostaglandins are widely used for terminating pregnancy, particularly in the second trimester.[104,105] Major complications of this treatment include bronchospasm, shock, seizures and cervicovaginal fistulas. Gastrointestinal symptoms are common. Prostaglandins are generally more effective, however, and are associated with less frequent serious side effects than hypertonic saline.[124] Side effects are also minimized with local administration (intrauterine or intravaginal instead of oral, intravenous or intramuscular) and with newer analogs.[125,126] Abnormal pregnancies, such as missed abortions and intrauterine fetal death, appear particularly sensitive to exogenous prostaglandins.[127]

Karim and co-workers in Singapore first reported the use of prostaglandins for inducing labor in 1968.[128] However, oxytocin generally remains the drug of choice.[104,107,129] NSAIDs may prolong gestation and delay the onset of labor. These drugs should not be used for treating cases of premature labor as they potentially affect fetal pulmonary circulation and hemostasis.[130] Endogenous prostaglandins may be involved in cervical ripening,[131] and exogenous prostaglandins have been used to hasten cervical ripening at term.[132] Prostaglandins may also be effective in controlling postpartum hemorrhage.

NSAIDs are an established therapy for closing a patent ductus arteriosus in premature newborns.[133,134] It is likely that prostaglandins (probably PGE_2 or PGI_2) function to maintain patency of the ductus during normal fetal life. These prostaglandins arise from ductal tissue or possibly from the lung. At birth, the ductus normally closes in response to increased oxygen tension, possibly related to a fall or a shift in prostaglandin synthesis.[135-137] Exogenous prostaglandins may be infused to prevent closure of the ductus arteriosus when it is critical to maintain fetal circulation, such as with congenital right ventricular outflow obstruction, transposition of the great arteries and with some anomalies of the aortic arch.[136]

Renal Function

There has been extensive research summarized by thorough reviews on the role of prostaglandins in renal physiology.[138-144] Prostaglandins have been implicated in the physio-

logic control of renal hemodynamics, renin release, sodium excretion and water transport. There are extensive data on possible functions of prostaglandins and thromboxanes in a number of renal diseases, including Bartter's syndrome, obstructive uropathy, functional renal impairment associated with liver disease, glomerulonephritis, acute and chronic renal failure and renal transplant rejection. In this review we will emphasize the clinical applications of these data, particularly the beneficial and adverse effects of NSAIDs.

Bartter's syndrome was the first renal disorder clearly recognized to involve augmented renal prostaglandin synthesis.[145-147] Increased renal synthesis of PGE_2 or PGI_2 from different regions of the kidney and peripheral vasculature contribute to the hyperreninism, sodium depletion, polyuria, low blood pressure, resistance to the pressor effects of angiotensin and norepinephrine, increased urinary excretion of prostaglandins and possibly to the hypokalemia. Administering indomethacin and other NSAIDs greatly alleviates these abnormalities, and NSAIDs are now the standard treatment. However, chloride wasting is likely the primary abnormality of this disorder and prostaglandins are probably secondary mediators. Giving NSAIDs does not fully correct the hypokalemia.[148] In patients with the more common disorders involving volume depletion or relative underperfusion of the kidneys, such as diuretic administration, surreptitious vomiting, congestive heart failure and cirrhosis with ascites, the increased prostaglandin excretion and prostaglandin-mediated hyperreninism are also reduced by NSAIDs.[143,144,149-153] Results of these clinical studies and of many animal and in vitro studies support the concept that prostaglandins (probably PGI_2 produced in the renal cortex) are involved in renin release, although prostaglandins are not obligatory intermediates, as profound stimuli arising from sodium depletion, β-adrenergic stimuli or hypotension causes renin release despite cyclooxygenase inhibition.[154-158] An additional clinical implication of these observations is that during renin determination for classification of hypertension or other conditions, NSAIDs will suppress renin activity and withdrawal of NSAIDs may cause a rebound elevation in renin.[159] Prolonged suppression of renin and the secondary suppression of aldosterone in some patients with mild chronic renal impairment may cause hyperkalemia and mimic the syndrome of hyporeninemic hypoaldosteronism.[160]

Synthesis of renal cortical vasodilatory prostaglandins is enhanced in patients with glomerulonephritis or underperfusion of the kidney, such as in those who have cirrhosis with ascites, heart failure or sodium depletion. These prostaglandins function to maintain renal perfusion, countering vasoconstrictor stimuli such as catecholamines and angiotensin. Administering NSAIDs to these susceptible patients unmasks the underlying renal vasoconstriction and results in an abrupt decrease in renal blood flow and glomerular filtration rate.* This situation is most dramatic in patients with cirrhosis and ascites in whom as little as 25 mg of indomethacin may cause anuria for several hours.[151-153] A diminished glomerular filtration rate may contribute to the apparent beneficial effects of NSAIDs to reduce proteinuria in patients with nephrotic syndrome, although a more direct prostaglandin effect on proteinuria may also be involved.[165]

*Reference numbers 143, 144, 151-153, 161-164.

The role of renal prostaglandins in sodium excretion is incompletely understood. Clearly, various NSAIDs cause sodium retention—generally about 150 mEq over several days in healthy subjects with greater retention in patients with various disease states.[166] The intrarenal site of action for this effect may involve active chloride transport in the ascending limb of Henle, sodium absorption in the cortical collecting tubule or reduced glomerular filtration.[138-141,167,168] The involvement of prostaglandins in sodium excretion is most pronounced during diuretic administration. NSAIDs including aspirin and sulindac greatly impair the natriuretic response to furosemide, spironolactone and other diuretics.[34,169-171] There is increasing evidence that prostaglandins are also involved in water excretion. A series of studies by Orloff and others suggested that prostaglandins produced in the collecting tubule may function as a negative feedback inhibitor on antidiuretic hormone-stimulated water reabsorption.[172-174] Although the interactions of antidiuretic hormone, cyclic AMP and prostaglandins are complex and not fully understood,[175] it is clear that NSAIDs contribute to water retention in humans and may contribute to dilutional hyponatremia. Alternatively, these drugs may be useful in reducing water loss in patients with central diabetes insipidus.[138,140] NSAIDs also decrease water loss in patients with nephrogenic diabetes insipidus, indicating that the drugs also act independently of antidiuretic hormone, apparently by altering the medullary or glomerular blood flow.[176]

A series of animal studies by Morrison, Needleman and associates have shown that a ureteral obstructed kidney produces large amounts of thromboxane A_2, which may increase renal vascular resistance and diminish renal blood flow.[177,178] A similar situation occurs after partial obstruction of the renal vein.[179] In these models, fibroblast and mononuclear cell infiltration is the source of the augmented thromboxanes.[180] Renal thromboxane production is also increased in experimental glomerulonephritis.[181] The role of vasoconstrictor thromboxane in human renal function is less clear. Thromboxanes do not regulate renal blood flow in normal persons.[182] Urinary TxB_2 is greatly increased in patients with the hepatorenal syndrome,[183] but thromboxanes are probably not the cause of the renal vasoconstriction.[184] In patients with renal transplant rejection, urinary TxB_2 is also increased and serves as an early indication of rejection.[185] In this disorder it is likely that thromboxanes from infiltrating cells contribute to the rejection process. Platelet generation of thromboxanes or prostaglandins may also have deleterious long-term effects on the progression of membranoproliferative glomerulonephritis in humans.[38]

Pulmonary Physiology and Diseases

In studies using pharmacologic amounts of eicosanoids in isolated tissues, animals and humans, possible functions of these chemicals have been suggested in regulating lung vascular and bronchial smooth muscle tone and in mucus secretion.[186,187] Although there are species and preparation differences, pulmonary vascular constriction is caused by PGE_2 (opposite to its peripheral vasodilatory effect), PGD_2 and $PGF_{2\alpha}$.[186-189] PGE_1 is a vasodilator, and administering a PGE_1 analog to patients with chronic lung disease is effective in lowering pulmonary vascular resistance but does not immediately improve pulmonary function.[190] PGI_2 is also a potent

vasodilator and weak bronchodilator, and infusions of PGI_2 have been administered for treating pulmonary hypertension.[191]

$PGF_{2\alpha}$, TxA_2 and PGD_2 are bronchoconstrictors, and the bronchoconstrictive effect of $PGF_{2\alpha}$ aerosol is greatly potentiated in patients with asthma.[187,192] In contrast, PGE_1 and PGE_2 are bronchodilators and block the effects of $PGF_{2\alpha}$.[193] As described above, leukotrienes C_4, D_4 and E_4 are extremely potent bronchoconstrictors, perhaps 1,000-fold more potent than histamine on bronchial tissue.[194-196] These leukotrienes also stimulate mucus secretion and increase vascular permeability.

These pharmacologic data are not synonymous with physiologic functions. However, there is strong evidence for eicosanoid activity in several types of pulmonary disease, particularly in patients with asthma.[197] SRS-A (now identified as peptide leukotrienes) has been implicated as a key mediator of allergic bronchospasm for decades.[198] These leukotrienes are synthesized in human lung tissue, especially from pulmonary mast cells.[199,200] Leukotriene generation is increased during an allergic challenge in patients with asthma in parallel with the onset of bronchoconstriction.[201] In contrast to their hypersensitive response to $PGF_{2\alpha}$, however, patients with asthma have the same degree of bronchoconstriction response to LTD_4 as do those who do not have asthma.[202] In guinea pigs, part of the leukotriene-induced bronchoconstriction is mediated by augmented TxA_2 release,[203] but in humans the leukotriene effect is independent of cyclooxygenase products.[204] About 15% of patients with asthma have an attack following ingestion of an NSAID, apparently related to cyclooxygenase inhibition[205] and possibly due to a shift in arachidonic acid metabolism from cyclooxygenase to lipoxygenase products. Corticosteroids are a well-established therapy for persistent asthma, and these drugs reduce lipoxygenase products, supporting the link between leukotrienes and asthma. Proof of this association and possible new therapeutic modalities must await development of specific leukotriene inhibitors.[43]

Eicosanoids have been implicated in several other types of acute pulmonary injury.[206,207] With massive pulmonary emboli, thromboxane release from activated platelets or lung parenchyma contributes to the hemodynamic alterations.[208] Assay of thromboxanes excreted in the urine may be a useful adjunct to diagnosing acute thromboembolic disease.[209] Thromboxanes and other cyclooxygenase products may also contribute to the pulmonary hypertension and respiratory distress that develops after trauma, fat emboli and possibly sepsis.[206,207,210,211] In studies of animals, cyclooxygenase and thromboxane inhibitors improve cardiopulmonary hemodynamics.[210-213] Infusions of PGI_2 or PGE_1 may also be useful by countering the effects of thromboxane, and clinical trials in humans are in progress.

Cyclooxygenase products are released into the circulation in large amounts during septic shock in animals and humans, and these products may also contribute to the systemic cardiovascular changes, including myocardial depression.[213-217] At least in some animal models of septic shock, pretreatment with thromboxane inhibitors improves survival.[214,216,217] The clinical usefulness of these agents for treating septic shock in humans has not been shown.

In inflammatory diseases of the lung, as with inflammation elsewhere, prostaglandins and leukotrienes are likely involved. During inflammatory insults, such as bleomycin administration and exposure to asbestos fibers, an interaction between alveolar macrophages and fibroblasts involving prostaglandin E_2 and interleukin 1 may lead to collagen production and pulmonary fibrosis.[218,219]

Gastrointestinal Physiology

Administering large amounts of prostaglandin E or F, such as for terminating a pregnancy, frequently causes diarrhea.[220,221] This phenomenon was initially attributed to direct stimulation of intestinal smooth muscle; it is now clear, however, that prostaglandins enhance intestinal fluid and electrolyte secretion and cause a secretory diarrhea.[222,223] Prostaglandins of the E and F type increase cyclic AMP in the small intestine and probably also in the colon, similar to the effects of cholera toxin.[224,228] Although still controversial, prostaglandins probably have only a minimal or secondary role in cholera toxin-induced diarrhea,[229] and prostaglandin inhibitors have not proved useful in treating human cholera infection. Endogenous prostaglandins may have a physiologic role in jejunal secretion in humans,[230] and augmented intestinal prostaglandin synthesis may contribute to the diarrhea associated with *Salmonella, Shigella* and *Escherichia coli* infections[231]; however, as in cholera infections, NSAIDs have not been clinically beneficial.

Prostaglandins have also been claimed to play a role in the diarrhea associated with a variety of noninfectious causes, including laxatives—such as bisacodyl, senna compounds, docusate sodium (dioctyl sodium sulfosuccinate)—thyrotoxicosis, hypergastrinemia, radiation-induced enteritis, irritable bowel syndrome and paraneoplastic syndromes.[224-226] It is difficult to interpret many of these early studies that suggested an association between prostaglandins and these clinical states. Some of the early prostaglandin assays of blood or intestinal contents were later shown to be problematic. The clinical response to NSAIDs often did not relate to increased basal prostaglandin levels. Studies done on animals were not always repeated in humans, and many publications were isolated case reports. In an excellent review, Metz, McRae and Robertson discuss the criteria to assess these publications.[232] Nevertheless, it is likely that overproduction of prostaglandins contributes to the diarrhea of a few patients with pancreatic tumors, medullary carcinoma of the thyroid and perhaps other conditions,[232,233] and a therapeutic trial of NSAIDs may be useful in patients occasionally seen who have diarrhea that is unresponsive to other modalities.

Prostaglandins are released at the sites of inflammation, including the colonic mucosa in cases of active inflammatory bowel disease.[234-236] These eicosanoids potentially may affect colonic motility, epithelial cell proliferation, anion secretion and inflammation.[234-237] However, administration of prostaglandin inhibitors does not appear to reduce the inflammation.[238-240] Conversely, administering prostaglandins does not appear to be effective in maintaining remission in patients with ulcerative colitis.[241] Lipoxygenase products are also increased in patients with colitis,[242,243] and these products may be more important than prostaglandins in contributing to inflammation and electrolyte secretion.[244] Recent studies by Stenson and Lobos have suggested that inhibition of leukotrienes is the mechanism of action of sulfasalazine and presumably corticosteroids in this disease.[245] The role of leuko-

trienes in inflammatory bowel disease will likely be further defined with the development of specific lipoxygenase inhibitors.

The most extensive research on prostaglandins and the gastrointestinal tract has focused on the gastric and duodenal mucosa. Early observations that exogenous prostaglandins inhibited gastric acid secretion in animals[246] and in humans[247,248] suggested that prostaglandins could be therapeutic agents for treating peptic ulcer disease. Synthetic prostaglandin analogs—especially 15,15- and 16,16-dimethyl PGE_2—were more potent and longer acting than the natural prostaglandins. In studies using animals, exogenous prostaglandins were effective in healing duodenal ulcers and protecting against gastric mucosal injury induced by acid, alkali, base and a variety of other noxious stimuli.[226-228,249,250] These protective effects, however, were obtained with doses of prostaglandins less than 1/100th the dose needed to reduce acid secretion. The term "cytoprotection" is used to refer to this ability of exogenous prostaglandins to prevent damage to the gastric mucosa from noxious stimuli. Extensive research into the mechanism of cytoprotection has ensued. There are experimental data to support and to refute each of the proposed mechanisms: increased gastric mucosal blood flow, stimulation of cyclic AMP, prevention of gastric mucosal barrier disruption—that is, reducing hydrogen ion diffusion back into the mucosa—stimulation of mucus secretion, increase in alkaline secretion from nonparietal cells—that is, increasing the mucus-bicarbonate barrier—stimulation of cellular protein synthesis or transport or stabilization of lysosomes, maintenance of sulfhydryl compounds, increased cell proliferation and increase in mucosal surface hydrophobicity. It is clear from numerous clinical trials in humans that orally administered prostaglandins are equally effective as H_2 antagonists in healing duodenal ulcers, and prostaglandin analogs will likely be available for general clinical administration for this indication within a few years in this country. These compounds include 16,16-dimethyl PGE_2 (Upjohn), enprostil (Syntex), misoprostol (Searle), rioprostil (Ortho-Miles-Bayer) and trimoprostil (Hoffmann-La Roche).[251] These agents may also prove useful in treating gastric ulcer and hemorrhagic gastritis. The drugs are not without effects in other organs, and there is evidence that they may potentiate esophagitis associated with reduction in lower esophageal sphincter pressure.[252,253]

Endogenous production of prostaglandins from the gastric mucosa functions as a physiologic protective mechanism.[226-228,249,250] Current theory is that mild irritants, such as dilute ethanol, sodium chloride solutions and acid, stimulate prostaglandin production, which protects the gastric mucosa from subsequent necrotizing agents (more concentrated ethanol, for example). This phenomenon may also contribute to the therapeutic effects of sucralfate[254] and antacids.

Prostaglandins are likely involved in other aspects of gastrointestinal function. Gallbladder production of eicosanoids is increased in the inflamed tissues of cholecystitis and may contribute to decreased fluid absorption, gallbladder contraction and biliary pain.[255] Endogenous prostaglandins may also be involved in intestinal motility, although the clinical relevance to humans has not been shown. However, exogenous prostaglandins may be useful in stimulating motility in the treatment of postoperative ileus.[256]

Metabolic Disorders

There is laboratory and hypothetical evidence implicating prostaglandins in many metabolic processes including hormone secretion, neurotransmission and mineral and electrolyte disorders. The topics of glucose regulation and hypercalcemia of malignancy have received the most attention.

The role of arachidonic acid metabolites in glucose regulation has been controversial.[232,257-259] Prostaglandin E is synthesized by the pancreatic islet, and infusions of prostaglandin E in humans generally inhibit insulin secretion and increase circulating glucose concentration. Although aspirin immediately enhances insulin release in persons with type II diabetes mellitus, available data fail to substantiate a clinically significant glucose-lowering effect in prolonged trials. Indomethacin has the opposite effect of other NSAIDs, apparently by a non-cyclooxygenase-mediated mechanism. Recent data suggest that a lipoxygenase product, probably 12-HETE, produced by the islet cells may have a key role in mediating insulin release.[260]

Prostaglandins were first implicated as mediators of hypercalcemia of malignancy in animal models.[261] Presumably a prostaglandin metabolite released into the circulation stimulates bone resorption, and indomethacin normalizes the hypercalcemia.[261] Recent findings have challenged this interpretation.[262] In humans, as many as 20% of cancer patients with hypercalcemia have no apparent bone metastasis, implicating humoral mechanisms for the hypercalcemia. An early study by Seyberth and associates implicated excessive circulating PGE, presumably released from the tumors, as the cause of hypercalcemia in many of these patients.[263] Administering indomethacin or aspirin reduced the serum calcium levels in the patients who had increased PGE metabolite levels. Other investigators have also shown increased prostaglandins and reduced serum calcium levels with indomethacin in a few patients[264,265]; it is not established, however, that circulating prostaglandins exist in high enough concentration to directly induce bone resorption. There is also evidence that the tumors may have products that induce the bone to synthesize eicosanoids, which then cause release of calcium.[266] At this time, the topic remains unclear, and circulating prostaglandins are probably not the explanation for the hypercalcemia of malignancy.[267]

Arachidonic acid metabolites have been implicated in other aspects of cancer, including immunosuppression, cancer cell growth and metastasis, and there is a potential use for NSAIDs in combination with chemotherapy. Several recent review articles discuss these topics.[268-273]

Conclusions

Because of the recurring history of prostaglandin research in which many proposed physiologic functions could not be confirmed with subsequent better methods and study design, our concluding comment is to emphasize that readers carefully evaluate the assay techniques, the use of pharmacologic agonists and antagonists and the protocol design before accepting newly proposed physiologic functions for eicosanoids.

Research in arachidonic acid metabolites has increased greatly over the past two decades. The discovery of leukotrienes and related compounds will likely lead to clinical benefit in patients with asthma and inflammatory conditions. In

1985, prostaglandins have definitely become part of the clinical practice of medicine, particularly in the fields of reproduction, gastroenterology, nephrology and rheumatology.

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Clinicopathologic Conference

Congophilic Angiopathy With Intracerebral Hemorrhage

Discussants
FRANCIS M. FILLOUX, MD, *and* JEANNETTE J. TOWNSEND, MD

JEANNETTE J. TOWNSEND, MD:* A 64-year-old man presented to the Salt Lake City Veterans Administration Medical Center for evaluation of apathy, diminished activity and speech difficulty with possible memory impairment developing three weeks before admission.

The patient was an occasional binge drinker. Three weeks before admission he "went on a heavy drunk." His family said that he had not suffered cranial trauma at the time. Following this 24-hour binge he was noted to be apathetic and had a very sparse verbal output. He said he did not have pain or discomfort. One week before admission a slight limp developed on the right side and he began feeding himself with the left hand although he was right-handed. He was brought to hospital by concerned family members.

This man had been a healthy building contractor. Mild organic heart disease with first-degree atrioventricular block had been noted two years previously, but no arrhythmias were recorded. A benign branchial-cleft cyst had been removed from the left side of the neck two years previously, and there was a remote history of hiatal hernia, appendicitis and nephrolithiasis. He was taking no medications and had smoked one pack of cigarettes per day for 35 years. There was no family history of cardiovascular, cerebrovascular or neurologic disease. A review of systems showed that he had undergone a voluntary weight loss of 7 kg over the previous year. His family also noted "slowness in thinking" over the same period of time, manifested primarily as difficulty in job performance.

On examination he was pleasant, slightly obese and apathetic, with profound cognitive impairment. He was afebrile and normotensive with a regular pulse of 68 beats per minute. The findings of the general physical examination were remarkable only for distant cardiac sounds. There was no sign of cranial trauma. He spoke with pronounced circumlocution with minimal spontaneous output. Although he knew where he was, he could not verbalize this. He had no idea of the date and could detail nothing regarding his past history or present circumstances. He could follow only the most simple (one-step) commands and manifested right-left confusion, perseveration and acalculia but not finger agnosia. He failed to recall any of three objects at five minutes. Cranial nerve function was intact, but a minimal pronator drift was present in the right upper extremity. Otherwise, muscle strength and tone were intact throughout, and muscle stretch reflexes were 2+ to 3+ and symmetric. Plantar responses were flexor. There were bilateral palmomental reflexes, but no other frontal release signs could be elicited. The patient's gait was mildly asymmetric with minimal circumduction on the right. A Romberg's sign was not present, and coordination was not impaired. Only simple sensory testing could be carried out, with no abnormalities.

Laboratory evaluation elicited the following: hematocrit, 50.6% with normal red cell indices, and platelet count, 226,000 per μl. The leukocyte count, prothrombin and partial thromboplastin times were normal, and a Westergren sedimentation rate was 20. Analysis of urine, a chemistry screen and a serum acid phosphatase level were normal, as was the chest radiograph. An electrocardiogram (ECG) showed small Q waves in leads II, III and aV_F and right axis deviation. An intravenous pyelogram, liver-spleen scan and a bone scan were also unrevealing, while an echocardiogram showed no thrombus.

An unenhanced computed tomographic (CT) scan of the head showed a hyperdense lesion in the left frontal lobe with a large surrounding hypodense area suggesting edema associated with mass effect and cingulate gyrus herniation (Figure 1A). With contrast infusion, a thin rim of enhancement was noted (Figure 1B). An electroencephalogram showed pronounced high-amplitude δ activity most prominent over the left frontal area, with some spread to the opposite hemisphere anteriorly.

Dexamethasone and phenytoin were administered, and

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
ECG = electrocardiogram

over the ensuing two weeks considerable improvement in cognitive function was noted. The patient remained normotensive throughout. A second CT brain scan done at this point showed some resolution of the previously described hyperdense lesion. The associated mass effect and edema were also diminished, but again rim enhancement was noted with contrast infusion (Figure 2). A brain biopsy was done.

Discussion

FRANCIS M. FILLOUX, MD:* The case of this 64-year-old man challenges us to provide an explanation for spontaneous intracerebral hemorrhage and offers the opportunity to discuss the differential diagnosis of intraparenchymal cerebral hemorrhage.

In considering the extensive differential diagnosis of intracerebral hemorrhage (Table 1), certain salient points of this particular patient's history need to be taken into account: the onset of the patient's illness was somewhat vague; the patient was not hypertensive, nor was he subject to known systemic disease; there was a history of mild cognitive dysfunction, and the hemorrhage was lobar in nature.

The temporal pattern of a neurologic disease is critical for the diagnosis. Events of an abrupt onset are usually vascular or epileptogenic in nature, whereas those of gradual onset are more characteristic of degenerative disease, tumors or infection. Unfortunately, the development of this patient's illness is far from clear. On the one hand, we are told of cognitive dysfunction antecedent to the patient's drinking bout. On the other hand, a somewhat abrupt change in personality and behavior was noted following his return to sobriety.

Certainly, central nervous system trauma is a well-recognized complication of alcoholism. Subdural hematoma is the most common lesion so encountered, but intraparenchymal hemorrhage is not inconceivable. Mitigating against this possibility, however, is the time course of the patient's illness. His first CT scan was obtained several weeks following his binge; at that time there was massive surrounding edema with subfalcian herniation. Had the bleeding taken place abruptly with a fall sustained three weeks earlier, the lesion could only have been larger initially, resulting in a far more serious presentation with greater impairment of consciousness or even death from transtentorial herniation.

This patient's disease did not present as a cataclysmic

TABLE 1.—*Differential Diagnosis of Nontraumatic Intracerebral Hemorrhage, in Approximate Order of Frequency*

Hypertension	Vascular hamartoma
Aneurysm	Arteriovenous malformation
Coagulopathy	Cryptic angioma
Blood dyscrasia	Cerebral amyloid angiopathy
Anticoagulant therapy	Hemorrhagic infarction
Tumor	Arteritis
	Mycotic aneurysm
	Cortical vein/dural sinus thrombosis

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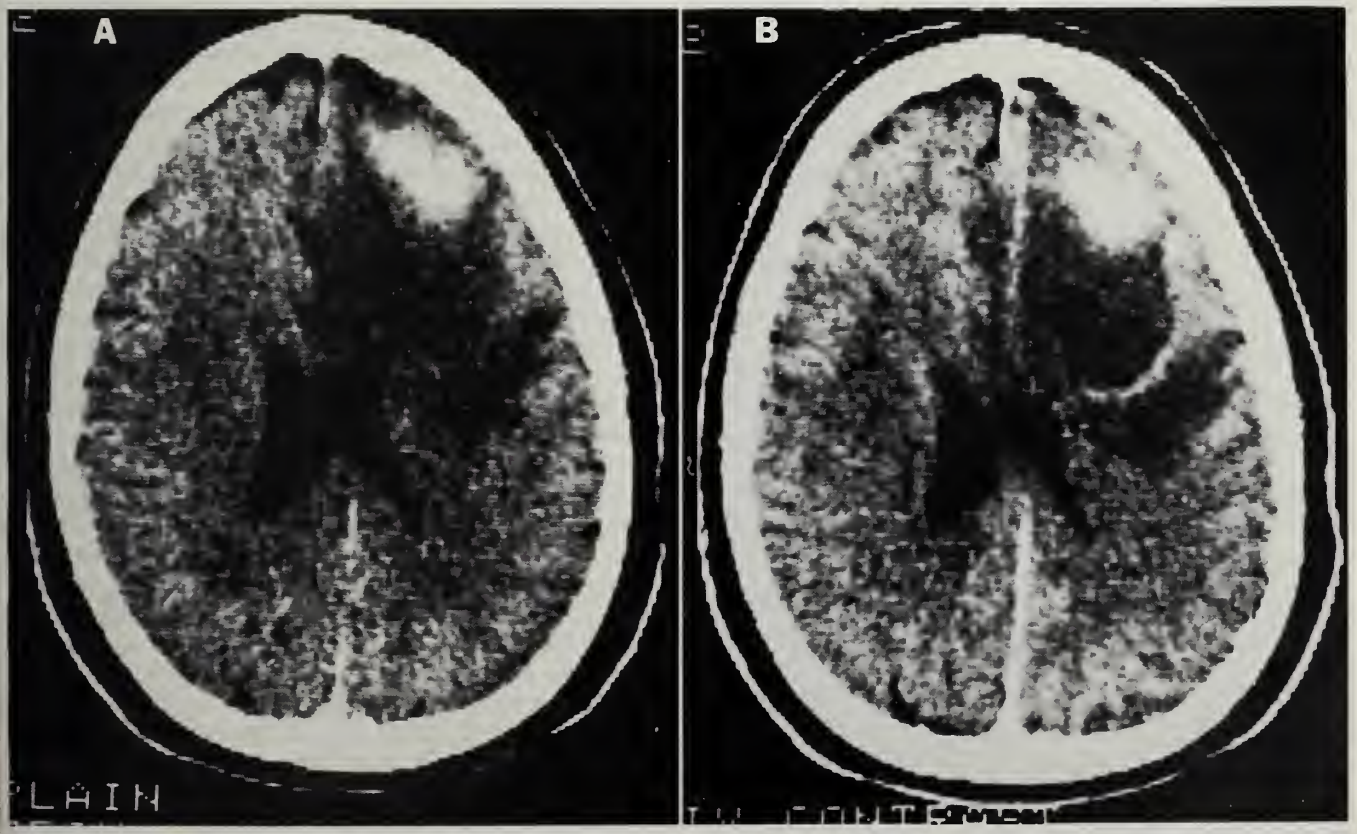

Figure 1.—Initial computed tomographic scans obtained three weeks after onset of symptoms. **A,** An unenhanced scan shows a hyperdense lesion with prominent surrounding edema and mass effect. **B,** A thin rim of enhancement appears with contrast infusion.

event typical of a ruptured berry aneurysm. Ruptured aneurysms account for the highest proportion of nontraumatic intracranial hemorrhages in some series.[1] These cause subarachnoid hemorrhage characterized by the instantaneous onset of severe headache and often followed by alteration of consciousness or focal neurologic signs. They commonly occur during physical exertion. Meningismus is generally present, and subarachnoid blood is encountered in most cases on CT scan or on examination of the spinal fluid specimen. All of these features are notably absent in our patient's case.

In rare cases, an appropriately located aneurysm may rupture directly into brain parenchyma, causing a lobar hematoma. The most common locations for such a bleeding event include the base of the frontal lobes and septum pellucidum as well as the temporal and frontal lobes immediately adjacent to the sylvian fissure.[2] The eccentric location of this patient's intracranial hemorrhage makes such a cause most unlikely.

In about 30% of cases, embolic strokes may be followed by hemorrhage into infarcted brain tissue. In such cases, however, focal neurologic deficits would be expected during the initial phase of the disorder, and a history of transient ischemic attacks would be usual. Not only were these features absent in this man's case, but the clinical evaluation failed to show a source of embolic material. An ECG showed no evidence of a previous myocardial infarction, and there was no history of a rhythm disturbance. The echocardiogram did not show a thrombus or valvular vegetation.

The patient did not have any historical or clinical evidence of hypertension, the leading cause of nontraumatic, massive intracranial hemorrhage. An elevated systemic blood pressure produces a structural alteration of the blood vessel wall leading to aneurysmal formation at arteriolar bifurcations. These weaken the wall, causing rupture. Hemorrhages resulting from this process commonly occur in the basal ganglia, although 10% may be lobar in origin. Such hemorrhages frequently extend into the adjacent ventricular system. The central location and ventricular involvement commonly result in stupor and coma with a generally poor prognosis. As can be seen, none of these features apply in this patient's case.

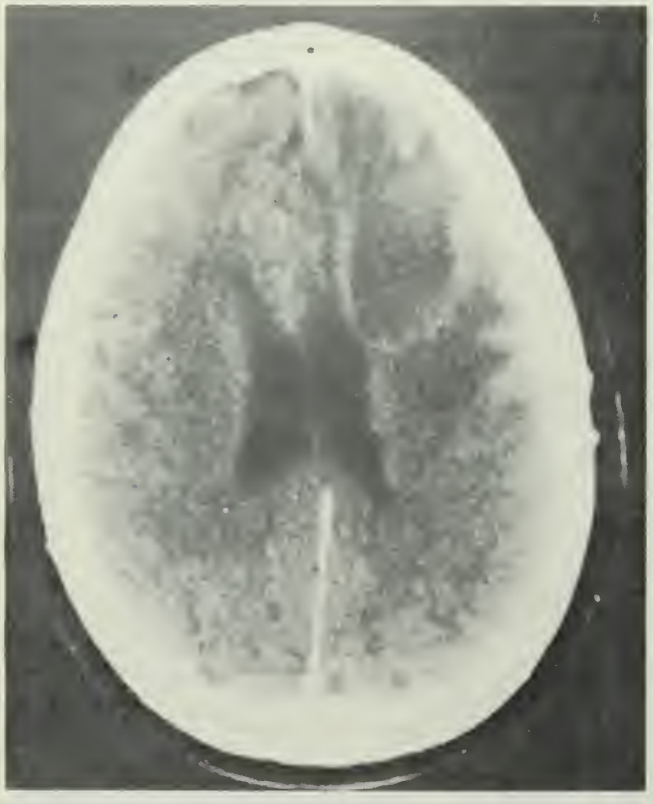

Figure 2.—A subsequent enhanced computed tomographic scan obtained five weeks after the onset of symptoms shows partial resolution of the hyperdense area and surrounding edema, but persistence of the thin rim of enhancement.

This patient was not subject to known systemic disease and we can exclude various hematologic conditions likely to cause lobar hemorrhages.[3] These include blood dyscrasias, coagulopathies and therapeutic anticoagulation. There was no evidence of leukemia or thrombocytopenia as his hemogram and coagulation studies were normal.

By this process of exclusion, we are left with three general etiologic possibilities: a vascular malformation, intratumoral hemorrhage and congophilic or cerebral amyloid angiopathy. In selecting one of these, we need to keep in mind the two remaining salient features of this case: the presence of antecedent cognitive dysfunction and the lobar nature of the hemorrhage.

At this point let us discuss the CT appearance of the hemorrhage (Figures 1 and 2). On the first scan there is a large, fairly homogeneous, high-density area in the anterior left frontal lobe. This is surrounded by an extensive low-density area of edema accompanied by a midline shift, compression of the adjacent ventricle and subfalcian herniation. With contrast infusion a thin, delicate rim of contrast enhancement is visible adjacent to the edematous area. Two weeks later the hyperdense area has nearly completely resolved and the surrounding edema has substantially diminished. The thin rim of enhancement persists.

In some cases the CT appearance of hemorrhage may belie its origin. For example, contrast enhancement in the case of hemorrhage from an angioma may show enlarged, abnormal vascular channels feeding or draining the hematoma. Intratumoral hemorrhage may be betrayed by a thick, irregular rim of contrast enhancement that is quite distinct from the thin, homogeneous rim of enhancement typically appearing about a spontaneous intracranial hemorrhage about a week following the onset of bleeding.[4] Frequently, however, the CT findings are quite nonspecific and angiography is most often disappointing, showing only an avascular mass corresponding to the hematoma. Even in the case of large arteriovenous malformations, several months must generally pass before angiography will show abnormal vascular channels.[5] For these reasons, an angiogram was not done in this case, and radiologic studies failed to elucidate a specific diagnosis.

Further difficulty arises in excluding from consideration the so-called cryptic vascular malformations, a term that bespeaks this lesion's ability to escape detection by the usual diagnostic methods. This category includes four pathologic disorders: capillary telangiectasias, venous angiomas, cavernous angiomas and small arteriovenous malformations. The first three are rare causes of intracerebral hemorrhage; the last is implicated only slightly more frequently. Their location, although most often in the distal middle cerebral artery territory, varies enough to be of little diagnostic import. Typically, however, these are encountered as a cause of hemor-

rhage in young people, occurring in children more often than in young adults, and nearly unheard of in the elderly.[6-8] Consequently, a cryptic angioma would be a conceivable but most unusual cause of this 64-year-old man's hemorrhage.

The two remaining conditions that could link cognitive dysfunction suggestive of early dementia and intracerebral hemorrhage include intratumoral hemorrhage and congophilic angiopathy. The former is not easily set aside. It is not an uncommon cause of nontraumatic intracranial hemorrhage, accounting for some 3% to 14% of such hematomas, depending on the series.[9-11] Although frequently heralded by focal neurologic deficit, seizures or known malignancy elsewhere, a cerebral neoplasm, either primary or metastatic, may present suddenly without prior warning as a central nervous system hemorrhage. The most common tumors include glioblastoma, metastatic lung carcinoma, choriocarcinoma and melanoma.[12] Although the CT picture may suggest the diagnosis by typical contrast enhancement (see above), an atypical location or a multiplicity of lesions, it is frequently nonspecific. In the case of this patient, the profound impairment of cognitive function following a year's history of intellectual decline suggested an infiltrative glioma of the frontal lobe. This possibility seemed likely enough to warrant brain biopsy to address the issue definitively.

On the other hand, a condition increasingly recognized as a cause of intraparenchymal hemorrhage in elderly persons is that known as congophilic or cerebral amyloid angiopathy.[13-15] This idiopathic condition is most commonly associated with dementia of the Alzheimer's type,[16] but has also been seen in cases of postradiation necrosis of the brain,[13] in an unusual demyelinating disease,[17] in persons with hereditary progressive ataxia with or without dementia,[18,19] in spongiform encephalopathies, adult trisomy 21[13] and in an hereditary Icelandic variety.[20] Amyloidosis of the cerebral vasculature is rarely associated with systemic amyloidosis and appears as an incidental autopsy finding with increasing frequency with age. It may be seen in 5% of nondemented patients in their seventh decade, 9% in the eighth decade and up to 17% in the ninth decade.[21] In a certain number (estimated at 3%[21]), cerebral amyloid angiopathy results in massive cerebral hemorrhage. The condition, in turn, may be responsible for a fair percentage of cases of nontraumatic intracerebral hemorrhage—as much as 9.3% in one autopsy series.[9] This percentage may increase as the incidence of hypertensive hemorrhages decreases.[22] Several Icelandic kindreds have been described in which spontaneous intracerebral hemorrhage occurs in early adulthood and is associated with amyloidosis of the cerebral vasculature, but not with clinical or pathologic features of dementia. This condition appears to be transmitted as an autosomal dominant trait.[20]

The characteristic hemorrhage resulting from cerebral amyloid angiopathy originates in the cortex or subcortical white matter and frequently dissects through brain tissue into the subarachnoid space. This particular location is favored because small and medium-sized leptomeningeal arteries are most often affected by amyloid deposition, and the pathologic process extends only a short distance into actual brain substance. Fibrinoid degeneration may coexist even in the absence of systemic hypertension. Presumably, the amyloid deposition results in vessel wall fragility and consequent rupture.[14,15] As might be expected, there is a tendency to repeated hemorrhage, varying both in location and in time of occurrence.[23-25] The changes of cerebral amyloid angiopathy tend to be diffuse and not confined to any given arterial territory; hence, hemorrhage may occur in atypical locations. Because of its peripheral location, the lobar hemorrhage of cerebral amyloid angiopathy carries a better prognosis than does the deep hemorrhage caused by hypertension. However, the presumed fragility of affected vessels suggests that surgical decompression or brain biopsy may carry an added risk and should be carried out with appropriate caution.

All the features of cerebral amyloid angiopathy and associated hemorrhage apply to this patient. A history of intellectual decline suggested possible early Alzheimer's disease. The hemorrhage was lobar in nature, in an atypical location and had evidently been tolerated well by the patient. There was no precipitating cause such as hypertension and no systemic disease. The lingering threat of hemorrhage into a glioblastoma led to biopsy, but certainly cerebral amyloid angiopathy provided an equally valid diagnostic consideration.

Pathology

Dr Townsend: The resected portion of the frontal lobe measured 3 by 2 by 1.5 cm and consisted of both gray and white matter with reddish brown discoloration.

On microscopic examination the tissue contained old blood clot with hemosiderin pigment and reactive tissue consisting of neovascularization and gliosis in the surrounding brain parenchyma. The subarachnoid space also contained hemosiderin pigment. Numerous small to medium-sized arteries in both the parenchyma and subarachnoid space showed homogeneously thickened walls that were positive with Congo red staining (Figure 3). Under polarized light they showed an apple green birefringence, confirming the amyloid nature of the material (Figure 4). Many medium-sized vessels in the subarachnoid space had a double-barrel lumen with subintimal proliferation (Figure 5). This feature has been noted by others in cases of congophilic angiopathy.[14] No neurofibrillary tangles or plaques were found in the surgical specimen.

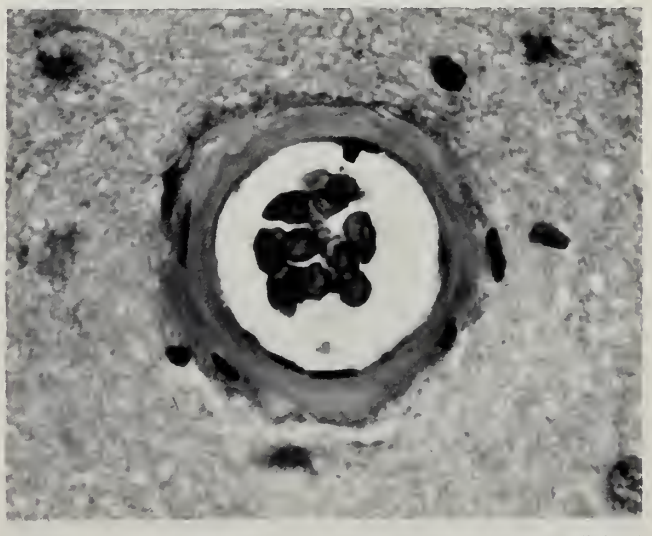

Figure 3.—A small artery with homogeneously thickened, hyalinized wall. Such arteries stained positively with Congo red (hematoxylin and eosin, original magnification × 100).

These findings confirm a diagnosis of amyloid angiopathy with hemorrhage into the frontal lobe and extension into the subarachnoid space. The age of the lesion is consistent with the onset of symptoms and there is no evidence of any acute bleeding.

The patient has done well since the operation a year ago. No subsequent hemorrhage has been reported, although about 10% of cases will present with recurrent hemorrhage.[25] The clinical presentation of mild dementia in this patient may be related to neurofibrillary tangles and plaques, even though none were seen in the biopsy specimen. It has been noted that as many as 30% of patients with congophilic angiopathy are demented and this has correlated well with the findings of neurofibrillary tangles and plaques at autopsy. These are usually most prominent in the hippocampus.

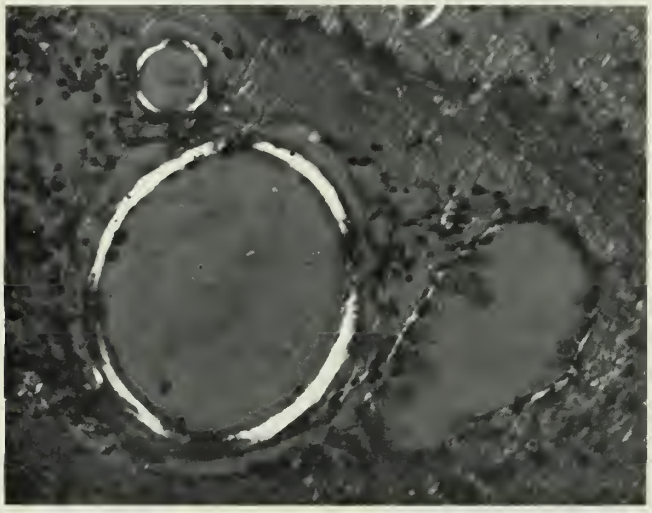

Figure 4.—Three small arteries whose walls show birefringence when photographed under polarized light (Congo red stain, polarized light, original magnification × 40).

Figure 5.—A meningeal vessel shows a characteristic "double-lumen" configuration described in cases of congophilic angiopathy (hematoxylin and eosin, original magnification × 40).

As with systemic amyloidosis, causative factors in cerebral amyloid angiopathy are poorly understood. Immunologic mechanisms are of course suspected. A recent study has reported evidence of lymphocyte dysfunction among persons affected by the Icelandic form of the disease. Specifically, there is an imbalance of lymphocyte subsets and reduced T-cell mitogenic reactivity. Aberrant membrane properties of these lymphocytes have also been found.[26] In this regard, the direct relationship of cerebral amyloid angiopathy to aging is intriguing, since decreased immune surveillance has been noted in other diseases of the aged.

In summary, this patient shows the typical clinical presentation and microscopic findings of congophilic angiopathy. Although the diagnosis must be confirmed microscopically, the onset of lobar hemorrhage in an elderly patient without hypertension should suggest the possibility of congophilic angiopathy.

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Primary Hepatocellular Carcinoma—Recent Advances and Future Prospects

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and formerly Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

CRAIG FITZ, MD:* *The topic for this Medical Staff Conference is "Primary Hepatocellular Carcinoma—Recent Advances and Future Prospects," and it will be discussed by Dr Alex Tseng. Dr Tseng attended the University of Chicago Medical School and completed his house-staff training here at the University of California, San Francisco. Following an oncology fellowship at Stanford University, Dr Tseng joined our faculty July 1983 as an Assistant Professor of Medicine in the Cancer Research Institute.*

ALEX TSENG, MD:† It is estimated that in 1985 there will be nearly 1 million new cases of cancer diagnosed in the United States.[1] Primary hepatocellular carcinoma, or hepatoma, is a relatively uncommon cancer in the United States, with fewer than 3,000 cases diagnosed each year. In contrast, hepatoma is a leading cause of cancer morbidity and mortality in large areas of Asia and Africa and may account for as much as 30% to 40% of all cancer deaths. Because hepatocellular carcinoma has unique geographic incidence rates throughout the world, it is considered to be environmental in causation, although the etiology almost certainly is multifactorial.

Hepatoma is usually an aggressive and rapidly fatal disease. Exciting developments, however, in the understanding of chemical carcinogenesis and the molecular biology of the hepatitis B virus (HBV) may provide new insights into the mechanisms of hepatic oncogenesis. With these advances, we can hope that new strategies in detecting, preventing and treating cases of hepatoma will soon be developed.

Etiology and Epidemiology

Cirrhosis

Patients with hepatocellular carcinoma have a higher incidence of cirrhosis of the liver, both micronodular and macronodular. Cirrhosis of diverse causes is associated with hepatocellular carcinoma. This includes cirrhosis associated with alcohol usage, hemochromatosis and α_1-antitrypsin deficiency. The cirrhosis of Wilson's disease apparently does not result in hepatocellular carcinoma.[2]

It has been calculated that hepatocellular carcinoma will develop in roughly 3% to 10% of patients with alcoholic or dietary cirrhosis in this country but that the rate may increase to at least 10% of all cases of macronodular cirrhosis, 20% for untreated cases of hemochromatosis with cirrhosis and as much as 40% of cases of cirrhosis caused by α_1-antitrypsin deficiency.[3]

Hepatotoxins

A major etiologic factor for the development of hepatocellular carcinoma is exposure to aflatoxins. Aflatoxins are metabolites of *Aspergillus flavus* and closely related fungi. They are very potent hepatocarcinogenic substances in virtually all animals so far tested.[4] There is a significant association between aflatoxin (AFB_1) contamination of staple foods and the high frequency of human liver cancer in many developing countries. In Nigeria and many other parts of Africa, peasants may ingest several times in excess of the maximum permissible level by the World Health Organization's standards.

In the liver cell, AFB_1 is metabolized by the microsomal mixed-function-oxidase system to generate AFB_1-2,3-epoxide, which is thought to be the main carcinogenic metabolite.[5] AFB_1-2,3-epoxide is highly reactive, is capable of tight covalent binding to DNA and RNA and may be an initiating step in carcinogenesis.

Other types of primary cancers of the liver are associated with drug exposure. These include angiosarcomas, whose cause is related to thorium oxide (Thorotrast), vinyl chloride and arsenic exposure.[6] In recent years, an apparent increase in liver cell adenomas has been associated with the long-term usage of oral contraceptives.[7]

Hepatitis B Infection

HBV infection is an underlying event preceding the occurrence of hepatocellular carcinoma in a large proportion of cases, with some estimates as high as 80%.[8] The latency period in humans is generally estimated to be about 40 years.

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
5-FU = 5-fluorouracil
HBV = hepatitis B virus
MR = magnetic resonance

In high-risk populations, the disease occurs in younger age groups and is more frequent in men. Throughout the world, most cases occur among persons who are HBV carriers. Many HBV carriers in the world were probably infected in early life by their own carrier mothers. It is estimated that 85% to 90% of perinatally infected infants have indefinite persistence of HBV.[9]

It is the survival and persistence of HBV in the population on a global scale that is responsible for a huge reservoir of carriers. Epidemiologic surveys by the Centers for Disease Control indicate that about 200,000 cases of HBV infection occur each year in the United States.[10] Between 12,000 and 20,000 people become carriers each year. At least 750,000 Americans and 200 million persons in the world are estimated to be carriers of HBV, with 80% now living in Asian countries.

A long-term follow-up study to determine the incidence of hepatoma in Taiwan was begun in 1975 by Beasley and coworkers.[11] In all, 116 cases of hepatocellular carcinoma were identified in 22,707 middle-aged men, 113 cases occurred among 3,454 carriers of the hepatitis B surface antigen and 3 cases occurred among 19,253 noncarriers. Thus, there was a 217-fold excess risk of hepatocellular carcinoma in carriers after 75,000 person-years of follow-up.

Similar epidemiologic studies have been done in the People's Republic of China, and reliable statistics are available from Shanghai.[12] Liver cancer is the foremost cause of cancer deaths between the ages of 15 and 44 years of age. Overall, it is the third most common cause of cancer mortality, after stomach and lung, and accounts for 14% of all cancer deaths.

What Is the Oncogenic Role of HBV?

Despite evidence of a strong association between primary hepatocellular carcinoma and chronic infection with hepatitis B viruses in humans, the relationship between the viral agents and neoplasia remains ambiguous. Varmus suggests three possibilities.[13] HBV may make a specific genetic contribution to oncogenesis by donating a viral oncogene or by mutating a cellular gene. HBV may act as a cofactor in tumorigenesis, such as by providing an ongoing stimulus for hepatic cell regeneration, with the possibilities of cellular mutations during subsequent replication. Finally, the presence of HBV may be merely coincident with the true carcinogens.

One approach to study the relationship between HBV and hepatocellular carcinoma is to use cloned HBV DNA as a specific probe to detect HBV DNA sequences in the liver and serum of diseased patients. The technique of transfer hybridization (Southern blot) has been used by Brechot and colleagues to determine the state of the viral DNA in the hepatocyte, either free or integrated in the host cellular DNA.[14] DNA analysis of tumors from patients with hepatocellular carcinoma has shown viral integration; to date, however, no consistent pattern of integration has been found.

Rearrangements of HBV DNA or cellular sequences (or both) in the host genome could lead to the production of hepatocytes with an abnormal phenotype (cellular transformation). A focal, clonal outgrowth of these cells could lead to an eventual hepatoma.[15] Studies characterizing this proposed sequence of events may ultimately be important in understanding the factors involved in malignant transformation. Recently, antibodies have been developed that are directed against a 28,000-dalton protein (p28) found in tissues infected with HBV. The presence of p28 in tissues infected with HBV and the appearance of specific antibodies in infectious serum specimens may correlate with hepatocellular carcinoma.[16]

Pathology

In regard to gross pathology, one of three macroscopic patterns is seen: a solitary, massive tumor; multinodular tumors, or diffuse infiltrating tumors. Figure 1 shows a multinodular tumor.

The tumor may be yellow-white or varying shades of green. Bile pigmentation is more often associated with hepatoma than with cholangiocarcinoma. Hemorrhage and necroses are particularly prominent in the unilobular form. All these tumors have a propensity for invading the hepatic veins. Histologically, cells can resemble normal hepatocytes. They

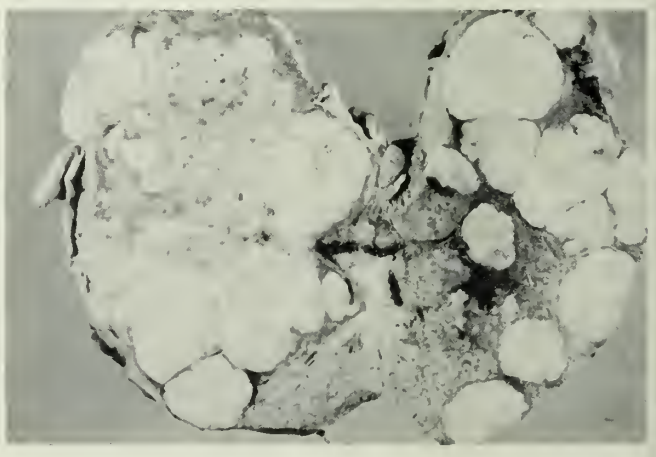

Figure 1.—Gross specimen of a multinodular hepatoma with background macronodular cirrhosis. (Courtesy of Martha Warnock, MD, Department of Pathology, University of California, San Francisco, Medical Center.)

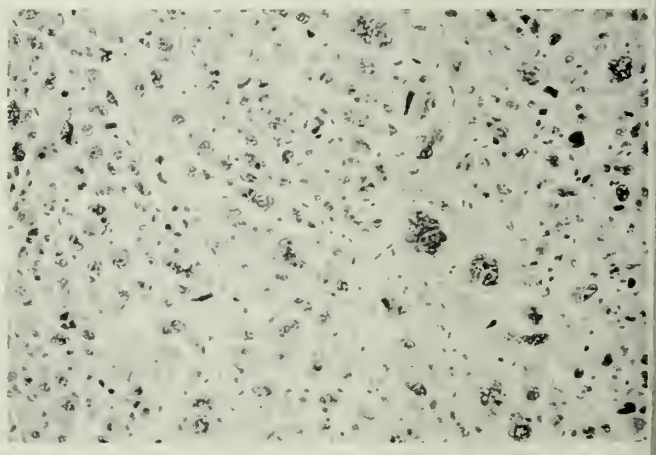

Figure 2.—Histologic picture of poorly differentiated hepatocellular carcinoma with anaplastic giant cells present (magnification × 250. Courtesy of Martha Warnock, MD, Department of Pathology, University of California, San Francisco).

can be well differentiated with cords and be separated by sinusoids. In less differentiated states, however, the cells appear as large, anaplastic giant cells (see Figure 2).

Clinical Manifestations

Signs and Symptoms

Hepatocellular carcinoma can progress rapidly and metastatic growth is commonly present, usually in the lungs, by the time a patient presents with signs and symptoms. Most patients with hepatocellular carcinoma will have right upper quadrant or epigastric pain of a chronic nature, accompanied by a right upper quadrant mass or a hard, enlarged liver.[17] This usually occurs in a patient with weight loss or increasing abdominal girth. It is not unusual for these signs and symptoms to occur in the presence of fever and jaundice.

Diagnostic Evaluation

The assessment of a patient with hepatocellular carcinoma should include methods to determine whether the patient has localized, resectable tumor, or whether the patient has extrahepatic metastases. In addition to a general physical examination, a complete blood count, liver function tests, α-fetoprotein level, chest roentgenogram and either an abdominal ultrasound study, a computed tomographic (CT) scan or a magnetic resonance (MR) imaging scan should be done.[18] Computerized, volumetric organ reconstruction of the CT or MR imaging scans may assist in quantifying tumor measurement.

MR imaging scans may also show involvement of tumor in the adjacent vascular structures. Finally, if a solitary mass involving one lobe is found, then a partial hepatectomy may be feasible, and arteriography should be done to determine the vascular supply.

General Medical Management

Lewis and Friedman have reviewed the various clinical presentations of cases of hepatoma and have described the common strategic mistakes in the care of such patients.[19] Special care must be taken with patients who have end-stage liver disease, with attention paid to hepatic synthetic function, possible precipitation of encephalopathy, associated cytopenias, coagulopathies, abnormalities in drug metabolism, fevers and paraneoplastic syndromes. From a physiologic perspective, hepatocellular cancer is a metabolically active tumor that can easily derange the fragile host environment. Physicians can do considerable harm unless they are aware of this complex milieu.

Prognostic Factors

Recognizing that hepatoma is a virulent cancer, are there prognostic factors that help discriminate between good and poor risk patients? Such discriminants would provide important information for the clinical care of an individual patient, the rational design of clinical trials and the careful interpretation of published studies.

The recognized prognostic features of importance include the state of the liver function and the patient's performance and also the histologic subtype.[20] Patients who have the fibrolamellar variant have a superior median duration of survival.[21] Pathologically, one sees deeply eosinophilic hepatocytes, intracytoplasmic hyaline globules and fibrosis arranged in a lamellar pattern. These patterns tend to be found in young women. Other factors such as α-fetoprotein levels, sex and geographic location have been analyzed as possible prognostic factors. It should be realized, however, that many of these factors are clinically interrelated and may not be independently significant.

Advances in Treatment

Surgical Treatment

If a patient presents with localized, resectable disease, a partial hepatectomy should be done. In selected cases, the five-year survival approaches 50%.[22] This compares with no five-year survivors for unresectable disease. Contraindications for partial hepatectomy include poor liver function test results, ascites, cirrhosis, extrahepatic metastases and bilobar involvement.

Scharschmidt has recently reviewed the experience of eight medical centers that collectively have carried out 819 orthotopic liver transplants since 1963.[23] In all, 155 patients have received transplants for hepatobiliary malignancy, and about 40% are still alive. Since 1983, 16 patients have had transplants in Hannover, West Germany, and in Pittsburgh, Pennsylvania, and the one-year survival probability is about 70%. Of course, longer follow-ups will be necessary before firm conclusions can be drawn.

Vaccination

Public health programs for HBV immunization are currently using vaccines that consist of subviral forms of the viral envelope that have been purified from the plasma of chronic carriers.[24-26]

In the United States, a safe and effective vaccine has been licensed, and equivalent vaccines are produced in France and the Netherlands. Vaccination trials are being conducted in Africa, Asia and Europe in the hope of controlling propagation of the chronic carrier state.

While such vaccines have established an excellent record, the expense, uncertain supply and the safety concerns associated with the plasma source have stimulated an intense interest in developing alternative sources of vaccine. Vaccines prepared by recombinant DNA and synthetic peptides methods have been shown to be immunogenic and protective in the chimpanzee model of human response. These vaccines have exciting potential as the next generation of HBV vaccines.[26]

Single-Agent Chemotherapy

For more than two decades, palliation of hepatoma patients with intravenous chemotherapy has been attempted. 5-Fluorouracil (5-FU) has been the most widely used agent. 5-FU is an antimetabolite that inhibits both DNA synthesis and RNA processing. Unfortunately, intravenous administration of a bolus of 5-FU has resulted in low partial response rates (6% to 10%).[26] There is reason to suspect, however, that prolonged intravenous infusions may be more efficacious, but no firm conclusions can be drawn at this time.[27]

Doxorubicin hydrochloride, an anthracycline drug that intercalates within DNA, is the single most effective agent for hepatoma patients. In pooling the results of six studies, doxorubicin induced an objective response in 64 of 240 patients (27%).[19] Not known is whether continuous infusions would offer greater effect. It should be noted that doxorubicin is metabolized principally by the liver and dosage reductions are

necessary in a patient with elevated bilirubin or hepatic alkaline phosphatase levels.

Combination Chemotherapy

Attempts to combine drugs to improve response rates and survival have been made. In general, combining doxorubicin or 5-FU with other drugs has not enhanced the effectiveness of either drug used individually.

Only the combination of doxorubicin plus 5-FU plus teniposide, an epidophyllotoxin, deserves further attention because an initial response rate of 44% was observed.[28]

The major criticisms of most studies of combination chemotherapy have been the relatively small number of evaluable patients and the lack of controlled trials. Therefore, larger, randomized trials testing more appropriate combinations of active drugs need to be done.

Intra-arterial Infusional Chemotherapy

It has long been recognized that liver tumors derive 90% of their nutrient blood supply from the hepatic artery. In contrast, normal hepatocytes are nourished predominantly by the portal venous system. Attempts have therefore been made to capitalize on this physiology to increase the therapeutic ratio by infusing drugs directly into the tumor via the hepatic artery. This will increase the local concentration of the antitumor agent and decrease systemic toxicity, especially if the agent is highly extracted on its first pass through the hepatic circulation.

The fluoropyrimidine drugs have a short half-life, less than ten minutes, but a high hepatic extraction ratio. For 5-FU, the hepatic extraction ratio after hepatic arterial infusion is 50% versus 30% for intravenous infusion. Even greater hepatic extraction is seen for infusions of 5-fluorodeoxyuridine (floxuridine [FUDR]), which has a 95% hepatic extraction ratio after hepatic arterial infusion versus 80% for peripheral venous infusion. Twofold to eightfold increases in hepatic drug exposure by hepatic arterial infusion are predicted for other drugs, including cisplatin, doxorubicin and dichloromethotrexate.[29]

Table 1 outlines the experience with single agents used intra-arterially. The majority of patients have received 5-FU or floxuridine. Although there have been no comparative trials of intra-arterial versus intravenous administration of fluoropyrimidine, the intra-arterial use of floxuridine appears to be superior.[30] Additionally, it appears that, given intra-arterially, doxorubicin and perhaps cisplatin may have similarly favorable pharmacokinetics and meaningful antitumor activity.[31] Although combinations of drugs given intra-arterially have also been used, it is not clear whether such combinations result in activity superior to floxuridine used alone.

The long-term administration of infusional chemotherapy once necessitated either a prolonged hospital stay or the wearing of a portable continuous infusion pumping device. Completely implantable infusion pumps have recently been developed that are highly reliable, have low morbidity and are able to administer long-term infusions into the hepatic artery.[38] However, this method of treatment should still be considered investigational because there is a spectrum of toxicities associated with intra-arterial therapy. Bleeding, occlusion, embolization and infection are recognized complications. In addition, the infusion of chemotherapy may also result in chemical hepatitis, gastritis, sclerosing cholangitis and small bowel ulceration.[39]

Last, occlusion of the hepatic artery has provided palliation to patients with hepatoma, and several studies have used intrahepatic artery infusional therapy followed by arterial ligation.[40]

Combined Modality Therapy

External radiation to the liver, while feasible, provides only limited benefit to patients with hepatoma.[41] This conclusion is based on the use of 2,000 to 3,000 rads as a single modality. However, the use of larger dose-fraction external radiation therapy may prove to be an effective means of symptom palliation without excessive risk of radiation hepatitis.

Friedman and co-workers in the Northern California Oncology Group have studied the combined use of infusional chemotherapy plus hepatic irradiation.[42] In a three-armed randomized trial, irradiation alone was compared with irradiation plus either intravenous or intrahepatic artery administration of chemotherapy. Responses were seen in 7 of 30 patients, with the greatest number in the patients receiving chemotherapy intravenously plus hepatic irradiation. The drugs were given by continuous infusion during the seven days of irradiation (300 rads daily), and toxicity was moderate (fever, anorexia, gastritis and anemia). Although response rates reached 35% to 50%, the mean duration of survival was only four months. Combined modality therapy, however, may be an effective induction regimen.

Two novel forms of internal irradiation are currently

TABLE 1.—*Intra-arterial Infusional Chemotherapy for Hepatocellular Carcinoma**

Authors	Drug	Dosage/Schedule	Patients Number	Partial Responses	Median Duration of Survival for Responders Months
Davis et al, 1974[32]	5-FU	15-30 mg/kg/d × 3 wk	9	NS	5
Pettavel and Morgenthaler, 1978[33]	5-FU	2-3 grams/d × 10 d then	11	NS	10
	Floxuridine	0.2 mg/kg/d × 12-24 wk			
Cady and Oberfield, 1974[34]	Floxuridine	0.3 mg/kg/d × 2-76 wk	18	8	20
Al-Sarraf et al, 1974[27]	Floxuridine	0.3 mg/kg/d × 3-74 wk	16	9	13
Wellwood et al, 1979[35]	Floxuridine	0.3 mg/kg/d × 8-50 wk	28	15	15
Olweny et al, 1980[36]	Doxorubicin	75 mg/m² q 21 d	10	4	
McIntire et al, 1976[37]	DCMTX	NS	8	0	

DCMTX = dichloromethotrexate 5-FU = 5-fluorouracil NS = not significant

*Modified from Lewis and Friedman[19]

under investigation. One method uses microspheres that are coated with radioactive yttrium and are injected into the hepatic artery for local deposition of radiation. Data are fragmentary with this approach.[43] Recently workers have investigated the use of isotopic immunoglobulin using antiferritin antibody in conjunction with standard external irradiation (2,100 rads) and intravenously giving doxorubicin plus 5-FU chemotherapy.[44] This approach is currently being studied by the Radiation Therapy Oncology Group and being compared with standard chemotherapy and radiotherapy. To date, 36 patients have been enrolled. It is too early to estimate and compare the median survival between treatment groups.

Future Prospects

The foregoing studies describe a range of active therapies. It is hoped that preventing transmission of hepatitis virus infection through widespread vaccination programs in endemic areas will decrease the incidence of hepatocellular carcinoma. In addition, further advances in orthotopic liver transplantation are expected. With chemotherapy, however, there have been no complete responses reported, and its impact on overall survival is still under study. Clearly, the discovery of new, effective single agents in phase II studies is desperately needed.

Infusional chemotherapy may permit more prolonged and precise drug delivery. Greater attention to the pharmacodynamics and pharmacokinetics of these drugs may improve the therapeutic index of doxorubicin, the fluoropyrimidines and other agents. Also of interest are additional ways to use radiation therapy in conjunction with chemotherapy, by changes in fractionation schedules or by the use of intrahepatic artery administration of radiation sensitizers.[19]

Progress in monoclonal antibody research should allow even more specific targeting of radioisotopes or drug-containing liposomes to hepatoma. Hepatomas have steroid hormone receptors and can respond to progestin therapy.[45] It may be possible to shrink tumors by relatively nontoxic hormone treatment. Finally, if the nature of the oncogenic stimulus becomes apparent through basic research in carcinogenesis and viral oncology, then it may become possible to develop highly specific drug therapy to block the oncogenic stimulus or, perhaps, to induce hepatoma cells to differentiate into a benign state.

Despite the considerable problems in the care of hepatoma patients, the future for investigation has never been brighter. There are many opportunities available for those who apply modern concepts of epidemiology, molecular biology, cancer pharmacology and radiobiology to improve the care of the hepatoma patient.

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Epitomes
Important Advances in Clinical Medicine

Occupational Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in occupational medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Irritant and Sensitization Effects of Formaldehyde

CLINICIANS NOT UNCOMMONLY ENCOUNTER patients with concerns about the relationship of a variety of subjective symptoms and formaldehyde exposure and sensitivity at home or in the workplace.

In October 1983 the Consensus Workshop on Formaldehyde brought together scientists from academia, government and industry to address the toxicology of formaldehyde. The workshop's panel on Immunology, Sensitization and Irritation reaffirmed that irritation of the eye and upper respiratory tract occurs but that a population threshold for this effect does not exist. Some sensitive persons may have sensory irritation at formaldehyde concentrations as low as 0.03 ppm, though most do not until levels are greater than 0.1 ppm. The ability of formaldehyde to produce skin irritation and allergic contact dermatitis was affirmed. Formaldehyde-induced contact urticaria has been documented on both an immune (type I allergy) and nonimmune basis. The workshop did not feel that sufficiently well-controlled scientific studies were available to establish that respiratory tract sensitization to formaldehyde occurs.

Pulmonary sensitization to formaldehyde may occur but is probably rare. In 1984 Reed and co-workers published a report of 13 patients with symptoms suggestive of asthma who had been exposed at home or work to formaldehyde ranging from 0.1 to 1.2 ppm. On bronchial challenge with 0.1, 1 and 3 ppm of formaldehyde for 20 minutes, no patient showed a significant (20% or greater) decline in forced expiratory volume in one second over 24 hours. Similar findings have been noted in persons with asthma, suggesting that even in preexisting asthmatic conditions formaldehyde at these concentrations fails to induce bronchial hyperactivity on an irritant basis. These reports contrast with that of Nordman and colleagues in 1985. A total of 230 patients occupationally exposed to formaldehyde was referred to the Institute of Occupational Health from all over Finland. Detailed medical and occupational histories were taken, spontaneous diurnal variations of peak expiratory flow were recorded and spirometry with bronchodilator, histamine provocation tests and bronchial challenges with 1 to 2 ppm formaldehyde and placebo were done. Of the 230 patients, 12 were considered to have bronchial asthma specifically caused by formaldehyde.

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Evaluating Infertility—Occupational Dangers to the Male Reproductive System

IN AN EARLIER ISSUE of the journal, Becker described male reproductive hazards, and this topic was later extended to workplace exposure. I will discuss two generally accepted approaches to evaluating gonadotoxic effects of occupational agents: assessing sperm quality and monitoring worker reproductive history by a brief questionnaire.

Full clinical assessment of sperm quality involves consideration of many complex factors. Examination of one of these factors, sperm count, has been the major sperm-related method for evaluating the workplace for gonadotoxic agents. As described by Whorton and co-workers, however, the method is psychologically invasive because one or more sperm specimens are required for analysis. Other important limitations and methodologic problems are discussed by Milby and Whorton. The method's principal advantage is that combining sperm count data with environmental exposure

measurements often shows recent contact with gonadotoxic agents.

Worker reproductive history is monitored by a questionnaire. This method involves retrospectively computing a standardized fertility ratio (SFR) derived from data on national birth probabilities. The SFR describes fertility before, during and after gonadotoxic exposure and differences are identified between exposed and nonexposed groups. A major advantage is its essentially noninvasive nature: questionnaire responses are limited to psychologically benign factors such as marital status, date of marriage and number, age and sex of children. Levine and colleagues have validated this method among workers exposed to dibromochloropropane and concluded that the questionnaire technique would have identified damage to the male reproductive system a number of years earlier than did the sperm count method.

Both methods generate valuable screening and evaluation data. The major difference is that the sperm count method is more useful for identifying recent gonadotoxic exposures, whereas the questionnaire approach provides a retrospective picture of male reproductive system damage. Both methods, however, provide useful tools for assessing the gonadotoxic potential of a workplace.

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Silicosis and Cancer Risk

ALTHOUGH THE ASSOCIATION between asbestos exposure and lung cancer has been well documented, silica exposure has not generally prompted concern about the excess risk of lung cancer. Recent evidence from both epidemiologic investigations and studies using animals has stimulated renewed interest in this association.

The findings of several studies of miners and foundry workers suggest that they have an excess risk of lung cancer. Those with relatively heavy exposure, such as furnace bricklayers and fettlers, appear to have the highest risk of excess lung cancer deaths. The specific role of silica is difficult to interpret, however, in that foundry workers are exposed to several potentially carcinogenic agents, such as polycyclic aromatic hydrocarbons (PAH), other organic compounds and metals such as lead, chromium and nickel. Some recent data suggest that there may be a synergistic interaction between silica and PAH in increasing the risk of lung and urogenital cancer. There is one group of workers, Vermont granite workers, who have a relatively isolated exposure to silica dust. Data from a 30-year cohort study of mortality in these workers suggest a slight but not significant increase in the incidence of cancer of the respiratory and gastrointestinal tracts and prostate and no relationship between amount of silica exposure and cancer risk.

Recent studies in animals suggest that silica alone may be a carcinogen. It appears that lifetime studies may be necessary to show tumorigenesis; perhaps this is why the association between silica and cancer has not been appreciated in earlier studies of experimental silicosis. Adenocarcinomas and squamous cell carcinomas have been induced in rats after either inhalational exposures or intratracheal instillations. Histiocytic tumors have been induced in rats by intrapleural inoculation of silica, which has also been found to act as a cocarcinogen with benzpyrene.

In summary, then, if there is an increased risk of lung cancer from silica, the risk is probably small and will be very difficult to prove conclusively. Important confounding variables in epidemiologic studies include smoking history, the concomitant presence of nonmalignant respiratory tract disease and occupational exposure to other dusts and carcinogens. Though studies in animals suggest that silica may be a carcinogen, there is a long latency, relatively heavy exposure may be necessary to elicit tumorigenesis and species specificity may be significant. Whether silica acts as a carcinogen alone, as a cocarcinogen or in some other capacity to enhance the risk of lung cancer remains to be determined. As new data emerge, evaluation of silica exposure standards may need to take into account the role of silica exposure in lung cancer risk.

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Surveillance of Hospital Personnel Exposed to Cytotoxic Drugs

MANY CYTOTOXIC DRUGS have been shown to be carcinogens or mutagens. In recent years, there has been a pronounced increase in the use of cytotoxic agents in treating cancer patients and, infrequently, patients with collagen diseases and psoriasis. In some patients who have had cytotoxic therapy, new malignant tumors have developed. Exposure to these drugs may prove to be occupationally health-hazardous in the case of certain hospital workers. Hospital pharmacists are involved in handling and preparing cytotoxic drugs, nurses and physicians in their administration and housekeeping staff in disposing of drug residues and products.

A few studies have been conducted relating chronic daily exposure to small amounts of these drugs to possible mutagenic or carcinogenic effects in the population at risk. Two methods have been used in assessing exposure to the cytotoxic drugs. First, the measurement of mutagenic activity in urine and, second, chromosome analysis for sister chromatid exchange and other chromosome aberrations of peripheral lymphocytes. Most studies indicate that personnel who were exposed to cytotoxic drugs had a greater number of chromosome abnormalities and increased sister chromatid exchanges or an increase in urine mutagenic activity.

Although these methods of assessing exposure to cytotoxic drugs have their limitations, and while better surveillance

tools are yet to be developed, these findings suggest the need for better precautionary measures to control unnecessary occupational exposures. Several guidelines have been developed concerning work with cytotoxic drugs. The principles of minimizing occupational exposure include good operational practice: the wearing of personal protective equipment (gloves, masks and clothing), the use of biologic safety cabinets (vertical laminar flow-containment hoods and bacteriologic glove boxes) and the proper labeling and disposal of cytotoxic waste products. Despite the use of precautionary measures, there is always a possibility of system failure and consequent exposure. Therefore, the need for biologic surveillance exists. Because of the large variability among persons, preemployment baseline measurement of sister chromatid exchange or urine mutagenicity may be more meaningful for exposure assessment to cytotoxic drugs than comparison of test results with normal population values.

The long latency period for the development of most cancerous lesions necessitates doing large-scale retrospective or prospective studies to determine cause-effect relationships between exposure and carcinogenesis. In the meantime, appropriate control measures should be exercised to protect hospital personnel who have significant daily occupational exposure to these medications. Other things being equal, the degree of exposure is a function of the amount of material being handled. Cytotoxic materials are handled in hospitals, free-standing clinics and physicians' offices.

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Video Display Terminals and the Eye

THE PUBLIC PRESS has suggested that many adverse medical effects occur from the use of video display terminals (VDTs). It has been reported that VDTs adversely affect the outcome of pregnancy and cause orthopedic and ocular problems, as well as possibly other problems. Only ocular problems will be dealt with in this article. The following paragraphs are modifications from a paper prepared by the American Academy of Ophthalmology.

A number of studies have been made by scientists at the Food and Drug Administration's Center for Radiological Health and Devices, Bell Laboratories and the National Institute of Occupational Safety and Health. The data from their work indicate that the VDTs "emit little or no harmful ionizing (eg, x-rays) or nonionizing (eg, UV [ultraviolet]) radiation under normal operating conditions." The emissions that were detectable were all well below the current national and international safety standards and were no greater than those produced by fluorescent lighting. In fact, the amount of ultraviolet radiation produced by VDTs is a small fraction of that produced by fluorescent lighting.

As for ocular damage, the best available current experimental and epidemiologic evidence does not indicate, or show, that the level of ultraviolet radiation emitted by VDTs is capable of exerting any deleterious effects on the ocular lenses of personnel using their terminals. Further, our own cornea and lens serve as natural filters for ultraviolet radiation, thereby protecting the retina, which is sensitive to low-level ultraviolet radiation.

Although there is no evidence that VDTs cause permanent ocular damage, in some work environments their use is associated with complaints of physical discomfort. These include ocular irritation (red, teary or dry eyes), fatigue (tired, aching heaviness of the eyelids), difficulty focusing (blurriness for seeing near or far objects), headaches, backaches and other musculoskeletal discomfort. Studies, particularly in Europe, indicate that most of these problems are related to poor ergonomic design of the workplace, lack of attention to the lighting and reflectance level of work surfaces, the type and intensity of the job demands and the quality of the video display. These can be alleviated by having the seating, angle of the VDT and so forth adjustable to each worker's comfort needs; by adjusting the lighting to minimize glare; by using high-quality monitors whose contrast and brightness can be controlled by the operator, and by making provisions for periodic rest breaks. In addition, eyeglasses worn by the workers, particularly those 40 years and older who have a reading or bifocal section, may need to be adjusted for the distance at which they view the VDT.

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Chronic Encephalopathy From Organic Solvents

ACUTE SYMPTOMS from organic solvent exposure resemble intoxication, ranging from simple depression or loquacious euphoria to slowed reflexes, dysarthria, dizziness, nausea, confusion, ataxia and even coma. Recurrent symptoms of intoxication associated with solvent exposure suggest the presence of chronic toxic encephalopathy analogous to that seen with long-standing ethanol abuse.

With repeated significant exposure, cumulative neuronal damage will produce gradual clinical manifestations of short-term memory loss, irritability, personality change, lethargy, impaired learning, impaired perception, depression and social withdrawal, all of which reflect a loss of cognitive abilities. There may be a history of eliminating or drastically reducing alcohol intake because of symptom exacerbation. Affected persons may frankly admit their diminished capacities or may confabulate or alibi to cover embarrassment. Although slowed peripheral nerve conduction can often be shown by measurement, clinical symptoms of peripheral neuropathy are less common. Dexterity and balance maintenance may be impaired.

Diagnosis requires recording the degree and pattern of cognitive impairment, and for this there is no substitute for the neuropsychologic test battery administered by a psychologist aware of the possibility. The standard clinical neurologic examination usually gives normal results, except for those responses that suggest impaired mentation. Electroencephalograms are usually normal. Advanced cases often show reduced cerebral size on a computed tomographic scan.

The prognosis is grim, especially if the offending exposures have happened over a considerable time period. Rehabilitative efforts can aid in coping with the problems of living. Investigators in Sweden have found that solvent-induced encephalopathy has occurred even though the solvent exposures were within the recommended limits. Because of the similarity of the clinical pictures, cases of presenile dementia should be screened with a careful occupational history in a search for chronic solvent encephalopathy.

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Cataracts, Ultraviolet Light and Occupational Exposure

OVER THE PAST TEN YEARS, there has been a growing recognition among ophthalmologic scientists that a major factor in the progression of the cataract of advancing age is ultraviolet radiation exposure.

The origins of this concept are based in epidemiologic investigations. In the 19th and early 20th centuries, Gross and Schulek first observed that cataracts were more common among people working in fields than in cities. This was confirmed by ophthalmologists in Hungary, Germany, Romania and Egypt. Furthermore, in dwellers near the equator (India, Pakistan, Africa and Central and South America) cataracts occurred earlier and at greater frequency when compared with those in the temperate zones of Europe and North America. Current studies add to the evidence. In the 1970s it was reported that cataracts occur earlier and more often in persons in Israel and India than in those in England or Scotland. In the United States, Hiller and colleagues reported that cataract prevalence is correlated with the number of hours of daylight determined from weather maps. Zigman and associates studied three geographical areas and showed that where the sunlight is brightest, brown cataracts occur at a higher frequency. In workers exposed to sunlight (farming, fishing, truck driving and construction) nuclear brunescent cataracts were found to develop much more frequently than in those who worked indoors. An analysis of 100,000 Australians (Aborigines and whites) recently showed a clear correlation between the prevalence of senile brunescent cataracts and levels of ultraviolet radiation.

Long-wave or near-ultraviolet light (300 nm to 400 nm) is now known to damage the ocular lens by inducing molecular changes in its proteins and by causing cytopathologic changes in its constantly actively growing epithelial cells. Laboratory studies have elucidated the molecular basis of sunlight-induced cataracts. Photon absorption by aromatic amino acids in lens proteins, particularly tryptophan, has been shown to be an initial event. Abnormal pigments with decomposed tryptophan accumulate as a brown, nuclear cataract. On the other hand, cortical cataracts may have a different pathogenesis, involving photolysis of membrane transport enzymes.

The inclusion of an ultraviolet-blocking molecule in the lenses of safety or operating-driving glasses would be effective prevention. There are 111 million American workers in occupations with cataract-inducing levels of ultraviolet exposure.

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Melanoma—An Occupational Hazard?

THE REPORTED INCIDENCE of skin melanoma is increasing among fair-complexioned people throughout the world. The increase is seen primarily between latitudes 45° north and 45° south. Higher levels of education and socioeconomic status, an indoor occupation, skin that sunburns easily, a history of melanoma or other skin cancer, dysplastic nevi and an increased number or size of moles are factors that correlate with melanoma incidence and in this sense may be thought of as "risk" factors.

Occupational factors have also been suggested as being contributory. However, when these suggested factors are examined among employee groups with comparable occupational exposure but in different geographic locations, consistency is lacking. At the First International Conference on Skin Melanoma, held in Venice in May 1985, neither the presentation of "Environmental Factors in Melanoma" by J. A. H. Lee, nor the subsequent discussions among the world experts in attendance implicated occupational factors as causal.

This leaves those concerned with melanoma the challenge of identifying factors possibly contributing to the increased frequency of melanoma diagnosis and of documenting possible causal relationships. Every practitioner of medicine must be vigilant in scrutinizing the skin of high-risk patients and seizing opportunities for the earliest possible detection of melanoma. Complete removal of thin lesions is almost always curative. Patient education is the cornerstone of early detection and consequent saving of lives.

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The Occupational History

MANY ARTICLES on occupational medicine remind physicians in other fields of the necessity of taking a good occupational history along with the medical history. Towards this end, various formats and styles of history taking are presented in the literature. Most tend to be highly inclusive, complex and cumbersome to use in daily practice. At the other extreme, a physican who does not use any routine or format may be lost early on and abandon the quest for occupational illness after the single inquiry, "What kind of work do you do?" And, finally, unless familiar with the field and legal requirements, many will not know what to do with the information gathered by using most available formats. The following format is presented to aid physicians both in taking a history and in directing them in the use of the information. The form should be used following a work history and positive response to general inquiry of exposure to substances and workplace environments such as asbestos, heavy metals, carcinogens, pesticides, noise, solvents, arsenic, ethylene oxide, dusts and radiation.

The format provides space for a general work description, exposure data and legal limits of toxic substances and required health surveillance in California. This format can be tailored to a particular area or population by adding or deleting specific exposure categories. It is best used when provided to patients in advance of their appointment so that reference can be made to work records for accuracy. However, it can also be used effectively when completed in the waiting room and reviewed with the examining physician at the same visit. It is most effective if maintained and compared from year to year on subsequent visits. The form is entitled "Interim Toxic

Cal/OSHA INTERIM TOXIC EXPOSURE HISTORY FORM TODAYS DATE:
WITH REFERENCE TO THE PAST THREE (3) YEARS:

NAME BIRTHDATE SOCIAL SECURITY #

OCCUPATION JOB TITLE JOB DESCRIPTION HOW LONG HELD

WORK RELATED INJURY OR INDUSTRIAL ACCIDENT?
PLEASE DESCRIBE:

EXPOSURE DATA: PLEASE BE ACCURATE

SUBSTANCE/CODE	EXPOSURES DATE, DURATION, AMT	PROTECTIVE EQUIP WORN: YES	PROTECTIVE EQUIP WORN: NO	ACUTE EFFECTS: YES	ACUTE EFFECTS: NO	LEGAL LMT: HR TWA/ceiling	In addition to a work & medical Hx and P.E., ADD: FOR THE EXAMINING ** DOCTOR
ASBESTOS/S208j						'action' 0.1 fiber /cc air PEL .5 fibers/cc	over 40: pa cxr, stool blood test, PFTs q1yr/ 3 view cxr q3yr under 40: pa cxr, PFTs q 1 year.
13 CARCINOGENS* S209g						NO DIRECT CONTACT	ANNUAL EXAM
VINYL CHLORIDE 3201k						1PPM/5PPM 0 ON SKIN	LIVER FUNCTION TESTS
DBCP/ S212m						1PPB/ 0 SKIN/EYE CONTACT	SERUM ESTROGEN/ SPERM CT; LH/FSH REPRODUCTIVE Hx
ACRYLONITRILE/ S213n						1 PPM	STOOL BLOOD, CXY DETAILED NEURO EX
MOCA/ S215k 4'4 METHYLENEBIS (2-CHLOROANILINE)						10ug/cc3/ air 50 surface: 100ug/cm	CXR PA,U/A,CBC, LIVER FUNCTIONS. MOCA URINARY TEST IF EXPOSED MORE THAN 10 YEARS.
EDB/ ETHYLENE DIBROMIDE S219k						130PPB 0 LIQUID	UNDEFINED AT THIS TIME on eye/skin
LEAD S215						50 ug/M3 "action" at 30ug/M3	ZPP,BLOOD LEAD, CREATININE,CBC. BUN,U/A.
PESTICIDES/ ORGANOPHOSPHATES.						Individual limits	RBC and plasma cholinesterase.
NOISE						90dBA/115	ANNUAL AUDIOGRAM 'action level' at 85dBA
RESPIRATOR USE	TYPE:	DATE:	WHY WORN:			FOR HOW LONG:	SPIROGRAM,EKG, HEARING/VISION
ARSENIC S214						'action' level 5ug	CBC,U/A,CXR PA, SPUTUM CYTOLOGY PEL 10ug/m3
EtO S220 ETHYLENE OXIDE						'action' 0.5ppm PEL 1 ppm	CBC, REPRODUCTIVE HISTORY

*13 CARCINOGENS: Acetylaminofluorene, Aminodiphenyl, Benzidene, Dichlorobenzidene, Dimethylaminoazobenzene, alpha-Naphthylamine, beta-Naphthylamine, Nitrobiphenyl, Nitrosodimethylamine, beta-Propiolactone, bis-Chloromethyl ether, Methyl chloromethyl ether, Ethyleneimine.

**For further information regarding periodicity of examination and details of followup of abnormal data, consult the individual Sections cited.

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Figure 1.—California Occupational Safety and Health Administration interim toxic exposure history form.

Exposure Questionnaire" and was developed for and is currently in use in periodic health surveillance examinations of the California Occupational Safety and Health Administration (Cal/OSHA) industrial hygiene and safety engineer inspectors by participating physicians at eight clinics throughout California (Figure 1).

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The Health of Refugees and Employment

IN THE WAKE of continuing civil and military strife and suppressive behavior by governments around the world, there has been an upsurge in immigration to the United States. In the two-decade span since 1961, a total of 7,815,000 people came to this country; in the five years from 1977 through 1981 alone, 2,651,000—or 34% of the total— arrived. Of particular health concern have been the more than 670,000 refugees immigrating since 1975 from Southeast Asia.

A variety of conditions has been documented at centers where numbers of refugees have been diagnosed and treated, including hepatitis B antigenemia, tuberculosis, parasitism (often with several agents), anemia, malnutrition, gonococcal infections and Hansen's disease. Internment before entry into the US has led to further health impairment. Subsequent study has disclosed primary resistance to antituberculosis drugs among Indochinese, the sudden unexplained nocturnal deaths among previously healthy men, dental problems, unfavorable pregnancy outcomes and a lack of understanding in the health care system of indigenous beliefs and practices involving self-care and attitudes toward, and expectations of, Western medicine.

While many of the immigrants have established their own businesses in big city enclaves, others have entered the labor market. With the passage of time and the acquisition of citizenship status, it is likely that there will be applications for employment among this group in manufacturing companies engaged in defense production. Both inplant health services and physicians conducting preplacement examinations should add certain case-finding procedures to their examination protocols that ordinarily are not included in the prehire evaluation or are not indicated in today's medical reviews of most job candidates.

The following procedures are suggested as components of the preplacement examination of refugees, particularly of those persons from Southeast Asia:

- A general physical examination.
- Tuberculin skin testing with subsequent chest radiography of persons having positive skin reactions. Referral to local or state health departments should be effected for the initiation of therapy. The Centers for Disease Control recommend further that a bacteriologic examination with smear culture and susceptibility studies be done in all suspected or follow-up cases.
- Serologic test for syphilis.
- Serologic test for hepatitis with forwarding of results when sources of general health and dental care have been established by the applicant or employee.
- Stool examination for intestinal parasites.
- Thick and thin blood smear tests for malaria for all persons with fever.
- Immunizations—tetanus toxoid, trivalent oral polio vaccine and others as indicated by age, previous immunization history or job assignment.

Particular clinical scrutiny must be conducted of food handlers, and appropriate treatment regimens initiated if parasitism involving *Giardia* and *Entamoeba histolytica* is encountered. Hepatitis B in a food handler presents a public health risk.

Certain culturally offensive practices should be avoided in the health assessment of Southeast Asian refugees:

- Complete disrobing of female patients (applicants or employees).
- Pelvic examination. This is usually not included in occupational medical practice, but, if indicated, it is not to be carried out on the first contact, and preferably should be done by a woman physician.
- Visible presence of an interpreter of the opposite sex during a breast or gynecologic examination.
- Negative judgmental attitudes toward traditional healing practices.
- Withdrawing numerous tubes of blood without proper warning or explanation.

As employment implies future visits to an occupational health facility, strict adherence to these recommendations will allow the establishment of trust and will ease further contacts required by either illness or surveillance programs.

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Health Risks in the Operating Room

ALTHOUGH HEALTH RISKS to patients undergoing surgical procedures have been widely recognized for many decades, it is only since the 1970s that the health risks to workers in the operating room have received similar attention.

There are several possible sources of health risk to operating room-based personnel. The most studied source is pollution from gases, which include volatile anesthetics, methyl methacrylate (used in surgical cements) and various sprays. Although more speculative, other sources include ionizing radiation, infection and stress. While causal relationships have not been firmly established, chronic exposure to anesthetic gases is most often implicated as the etiologic agent of increased risk.

Epidemiologic studies have identified several possible health hazards to operating room personnel. The most widely studied effects deal with reproductive outcomes. For example, it is generally accepted that female staff working in the operating room have a spontaneous abortion rate about twice that of various control groups. The results are equivocal for

the wives of exposed male staff. Similarly, there are conflicting results concerning other reproductive outcomes such as congenital anomalies in offspring, sperm abnormalities, infertility, stillbirths and altered sex ratio.

Other health risks associated with operating room exposure include cancer (such as leukemia and lymphoma), hepatic disease (besides hepatitis B), suicide and impaired psychomotor abilities. Again, these results are not consistent among the various studies and the case for increased risk has not been proved.

Unfortunately, many of these epidemiologic studies suffer from similar shortcomings—namely, their retrospective design, heavy reliance on questionnaires and grossly inadequate exposure data. Moreover, many studies were done before the use of newer anesthetic agents and modern gas scavenging systems. Thus, only a few associations appear to be valid today and contemporary, well-designed studies are warranted.

Nonetheless, recently developed technologies should be used to reduce the health risks to these workers. Specifically, personal dosimeters for gases and radiation should be used. In addition, protection from ionizing radiation (including thyroid shields and leaded glasses) should be available and the ambient levels of trace anesthetic gases in the operating room should be evaluated and minimized. Clearly, continued monitoring of these health workers is justified.

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Use of Personal Respiratory Protective Devices (Respirators)

"CAN THIS WORKER safely use a respirator?" is a question that clinicians are frequently asked. While it would be optimal to eliminate or completely enclose all workplace inhalational hazards, it is frequently necessary to rely on respirators worn by a worker for protection. These devices range from simple disposable filter masks to complex, heavy, self-contained breathing apparatuses such as those used by fire fighters.

Several factors affect medical fitness for using respirators. Certain physical characteristics such as weight may preclude their use. Certain respirators may impose loads on the respiratory or cardiac systems or both. A recent report suggests that as much as 10% of workers may have psychological problems regarding their use. The use of contact lenses while wearing respirators needs careful consideration. Finally, appropriate safety orientation and a worker's knowledge of the chemical hazards to which she or he is exposed is important. The recently enacted federal Right to Know Law mandates such worker training about chemical hazards for workers in many industries.

Fortunately, most respirators are well tolerated by most workers, and an extensive medical evaluation is rarely needed. Clinicians can frequently obtain information about respirators and the hazards against which they protect from a plant's occupational health service or industrial hygienist. Governmental (such as the Occupational Safety and Health Administration [OSHA]) and private or university consultants can also be of help. Finally, directly observing a worker using the respirator may be invaluable.

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Employee Drug and Alcohol Abuse—Industry's Approach

THE ANNUAL COST to industry of employee drug and alcohol use has been estimated at as high as $16.4 billion. A confidential mail survey of national organizations conducted in 1981 found that 80% of the respondents had to deal directly with drug problems. While alcohol was the most commonly abused substance (82%), marijuana incidents occurred in more than half the firms (55%) and both heroin and cocaine use was reported by a fifth of the organizations. The survey confirmed that drug usage in the workplace is relatively widespread and is not confined to blue collar or minority groups.

Employers use a variety of means to combat employee drug and alcohol use. A prerequisite to any technique is the development of a company policy outlining an organization's position on drug and alcohol abuse. The most widely accepted procedure is the establishment of an occupational treatment program whose primary target is workers whose job performance is impaired. This employee assistance program is a confidential service that intervenes with troubled workers, whether self or supervisor referred. It assumes that an employee's value to the organization is based on substantial training and time investment, a value that frequently does not extend to the youthful abuser. Young employees, having a different work ethic, do not respond favorably to constructive confrontation. Intervention varies with the particular program from simple triage to diagnostic evaluation, motivation, referral and follow-up. The treatment—normally subsidized by the company but provided at an accredited treatment facility not usually affiliated with the firm—is considered a condition of continued employment. Most employee assistance programs, however, reach only 5% of the target population.

Another method of providing a drug-free workplace involves urine drug screening on all employment applicants and selective screening of suspected abusers. Urine toxicology screening is an effective test to determine the presence of drugs in the urine. Thin-layer chromatography and radioimmune assays or modified techniques, such as the enzyme multiplied immunoassay technique, test for a wide spectrum of drugs including marijuana, phencyclidine hydrochloride, heroin, opiates and amphetamines. A great deal of weight is often placed on positive findings; however, the test does not provide information about the pattern of use and cannot distinguish between an occasional user and a chronic abuser. The

cost-effectiveness of this approach can be improved by limiting the tests based on the results of the preemployment medical examination.

There are serious questions about the reliability of the results of screening urine for drugs. In a recent evaluation of the performance of 13 laboratories, error rates for barbiturates, amphetamines, methadone, cocaine, codeine and morphine ranged from 11% to 94%, 19% to 100%, 0% to 33%, 0% to 100%, 0% to 100% and 5% to 100%, respectively. False-positives ranged from 0% to 6%, 0% to 37%, 0% to 66%, 0% to 6%, 0% to 7% and 0% to 10%, respectively. These results suggest the need for monitoring the performance of organizations and contract laboratories with blind quality-control samples. All urine toxicology screening tests require confirmation by an alternative method before being considered positive. Where punitive action is contemplated, additional tests may be necessary to accurately quantify urine and serum drug levels.

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AIDS—Management of Hazards to Health Care Personnel

ALL PATIENTS with the acquired immunodeficiency syndrome (AIDS) will require hospital or outpatient care or both during their illnesses. A wide variety of health care personnel, therefore, face emotional and infection hazards that must be carefully addressed. In addition, Centers for Disease Control (CDC) surveillance has shown that 3% of patients with AIDS are health care personnel (although none has been "linked to a specific occupational exposure"). Special attention must be given to these workers and to (1) those in AIDS risk groups because of life-style and (2) those who have other immunosuppressing conditions.

Available evidence about human T-cell leukemia virus III transmission has led to the design of infection control guidelines very similar to those for hepatitis B. Highlights include the following:

- Assume that every patient has *some* occult infectious disease.
- Slow down and *think* when using, manipulating or disposing of needles.
- Wash hands, even when gloved.
- Wear protective eye wear during suctioning or endoscopy if aerosols or flying debris may be produced.
- Disinfect surfaces with a bleach solution (1:10).
- Reevaluate requirements for mouth-to-mouth practice during cardiopulmonary resuscitation (CPR) certification and have resuscitation bags and airways immediately available for AIDS patients who desire CPR.
- Follow established hepatitis B protocols after AIDS exposures and give indicated hepatitis B prophylaxis without delay.

Support of staff members who may be fearful, exhausted, uninformed or grieving is as important as infection control. Fortunately, hospitals have social workers, chaplains, psychiatrists and psychologists and access to outside groups and can therefore design educational and counseling programs for individuals and groups. Additionally, policies must be designed to address the special requirements of pregnant personnel and immunosuppressed employees with patient care or particularly demanding responsibilities. Finally, confidentiality must be respected.

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Editorials

On Violating Promises

SOME MONTHS AGO *American Medical News* reprinted an article by Harry Schwartz that had been published by *The New York Times*. It pointed out that, of all Americans, doctors who treat Medicare patients are the only ones legally compelled not to raise their fees. It was his opinion that doctors are getting a raw deal, and surely there is support for this opinion among physicians. He went on to point out that the mandated freeze on these physicians' fees violated "openly and plainly" the promise made to physicians when the Medicare law was passed in 1966, and speculated on what might happen if government promises made to other citizens were also to be violated. He notes that "when government openly and enthusiastically violates its promises to one important group of Americans—doctors—the precedent has been set for violating promises to others" and asks "if breaking promises to doctors is all right, then what's wrong with breaking promises to 'rich' people who own government securities," for example.

These are times when what happens in health care may be a bellwether for what could happen elsewhere in our society. As Schwartz points out, government has made many promises to many people over the years, and when these are not kept, for whatever reason, trust in government and therefore in the American system becomes eroded, with eventual economic and political consequences no one really wants to think about. Schwartz's point could prove to be an important one, or so it seems to this writer.

MSMW

Navigating the Sea of Eicosanoids

"PROSTAGLANDINS, THROMBOXANES AND LEUKOTRIENES in Clinical Medicine" by Zipser and Laffi introduces the fundamental concepts critical to an understanding of the structural diversity and functional complexity of eicosanoid metabolites of arachidonic acid. Many of the metabolites generated by the enzymatic actions of cyclooxygenases and lipoxygenases on arachidonic acid are potent mediators of cellular and organ system responses that have potentially important roles in physiologic processes and disease states. The combined effects of multiple eicosanoid mediators that differ in action and potency often determine the overall biological response. A further element of adaptability is provided by the varied mechanisms of recognition and regulation of the mediators by target cells.

Generation and biodegradation of some products of the oxygenation of arachidonic acid involve one or more cell-cell interactions. For example, some 15-lipoxygenase products from eosinophils, epithelial cells and endothelial cells stimulate 5-lipoxygenase activity in mast cells and inhibit that expressed in macrophages and neutrophils.[1,2] The 5-hydroxy-eicosatetraenoic acid (5-HETE) released by neutrophils, macrophages or mast cells may be converted to double oxygenation products by 15-lipoxygenases of eosinophils or 12-lipoxygenases of platelets in mixed cell populations.[3] Cellular cooperativity not only leads to the production of novel dihydroxy and trihydroxy eicosanoid mediators with distinct activities, but also enhances the generation of mediators by any one type of cell through stimulatory factors released by another cell. In addition, some cells appear to degrade eicosanoid mediators released by other cells engaged in active synthesis. C-6 peptide leukotrienes synthesized by macrophages or mast cells are inactivated by halide-dependent peroxidases released from eosinophils.[4] Knowledge of these concerted synthetic mechanisms and pathways of degradation is critical to the interpretation of data from in vitro studies of isolated cells in relation to their significance in vivo.

A separate set of stereospecific receptors on target cells transduces the effect of each eicosanoid mediator.[5-7] Some target cells express subsets of receptors for a single mediator that transduce different functional responses. For example, human neutrophils have a high-affinity subset of receptors for leukotriene (LT) B_4 that are coupled to activation of chemotaxis and increased adherence and a low-affinity subset that elicits release of lysosomal enzymes and enhanced oxidative metabolism.[8] Thus, two concentrations of an eicosanoid mediator may interact with even one type of cell through different receptors with qualitatively distinct consequences. The choice of a pharmacologic antagonist may require estimation of the expected concentrations of such mediators for optimally specific competition at the receptor level.

The presence of different eicosanoid receptors that transduce specific effects suggests the possibility of finding biologically opposite effects of two eicosanoid mediators generated by the same pathway in one tissue. Thromboxane (Tx) A_2 and prostaglandin (PG) I_2 are generated when platelets adhere to damaged vascular endothelium. TxA_2 stimulates vasoconstriction and platelet aggregation, whereas PGI_2 promotes vasodilation and inhibits platelet aggregation. Thus it may be difficult to predict the results of inhibition of the shared pathway that produces TxA_2 and PGI_2 unless differences exist in the susceptibility to inhibition of activity of later synthetic steps. Opposite actions of a single mediator are sometimes identified in different types of target cells. For instance, LTB_4 stimulates the functions of T-suppressor cells and inhibits those of T-helper cells in vitro.[9] In other organ systems, the effects of eicosanoid mediators are additive or synergistic.

Some eicosanoid mediators act as second messengers for the primary actions of other eicosanoids. LTB_4 acts principally to augment the leukocytic components of inflammation. It also evokes bronchospasm, although with far lower potency than LTC_4 or LTD_4. The mechanism of transduction of the weaker effects of LTB_4 involves stimulation of the cyclooxygenation of arachidonic acid by target tissues, which leads to local generation of the potent bronchoconstrictor TxA_2. Inhibitors of cyclooxygenation thus may suppress the effects of 5-lipoxygenase-derived mediators.[10-12] In some instances, eicosanoids may condition the responses of tissues to other

eicosanoids and other mediators. LTE_4 alone stimulates bronchoconstriction. However, at concentrations below the threshold for a direct response, LTE_4 enhances bronchial reactivity to other bronchoconstrictors such as histamine.[13] Similarly, intradermally administered LTB_4 has the capacity to induce hyperalgesia, which augments the perception of subsequently applied noxious stimuli.[14]

The duration of exposure of a target tissue to any concentration of an eicosanoid mediator may modify the nature and magnitude of the response. Neutrophils preincubated with LTB_4 will later be less chemotactically responsive to this mediator due to a down-regulation of the number of high-affinity receptors.[8] Effects such as these may be relevant in disease processes such as adult respiratory distress syndrome, where pulmonary edema fluid contains greatly increased levels of LTD_4 and LTE_4 for many hours.[15] In spite of this, these patients do not show evidence of bronchospasm. This suggests that the airway smooth muscle is in a selectively refractory state, while the endothelial-epithelial cell network responds appropriately to the LTD_4 and LTE_4 with altered permeability and fluid transudation.

The principal task that must precede major pharmacologic manipulation of arachidonic acid metabolism in many complex diseases is the determination of relevance of elevated concentrations of potent eicosanoid mediators in tissue fluids. Chromatographic and immunochemical techniques of measurement and identification of the mediators are now available for sensitive and accurate assessment in disease states. In most diseases where tissue concentrations of the mediators are elevated, it is not known if they are primary pathogenic factors, secondary accessory elements or irrelevant reflections of the underlying condition. The results of carefully defined studies in vitro and in animals may help to resolve these issues.

Drugs can be developed that will affect the generation, activity and metabolism of eicosanoid mediators. The current dilemma and the opportunity, which are inextricably intertwined, are that drugs must be developed as pharmacologic probes in order to establish any involvement of the mediators in pathogenesis. Although the results of such studies may relegate the drugs to obsolescence immediately, the wide tissue distribution and the protean effects of these mediators favor the inevitable establishment of multiple physiologic and pathologic roles for the eicosanoids.

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Caring for the Poor

THERE IS an aspect of competition, whether in business or health care, that has been receiving relatively little attention of late. Those who lose out in the competition are left pretty much to fend for themselves. It is one thing if they are healthy, physically and mentally able to compete again, but another if they are not. Through most of history the sick, ailing or unfit have received short shrift, sometimes even at the hands of the medical profession. Darwin's law prevailed. The fit tended to survive and to succeed while the unfit did not. But modern medicine and modern social philosophy began to change all this, at least in western nations. Modern medicine made it possible to do more for the sick and unfit, and the new social policies tried to make the new health care available to all who needed it. The pendulum swung toward a more egalitarian approach, whether toward women, minorities, the disadvantaged or the unfit. Then, particularly in health care, the costs rose, and in the name of competition (to help reduce costs) the profit motive was blessed for the delivery of health care. But predictably, it is not proving profitable to provide health care for people who cannot pay for it. Both the private sector and government are now backing off from adequately financing health care for the poor, and there is now beginning to be evidence that at least some of the poor are not getting all the care they need, at least as soon as they need it.

So far this has not surfaced as a very large problem. Perhaps much of the health care now being rendered is not really necessary. Perhaps the poor or the unfit are not organized enough to protest the short shrift they are apparently receiving. Maybe we are moving de facto toward identifying an acceptable basic, frill-free or "generic" health care that will prove adequate enough though much less costly. In any case, there are not yet any inescapably persuasive data that indicate the health of the poor or unfit to be significantly worse as a result of their being victims of the competitive approach to financing health care in this nation. But the competitive process has not yet run its full course, and government has not yet cut back on financing health care for the poor and unfit as far as it no doubt will. But it would seem predictable that at some point things will get bad enough so that the conscience of America will be pricked again and, once more, something will be done about health care for the poor.

Physicians and the medical profession are personal advocates for patients and the professional advocates of good health care for all who need it. To take on both the private sector and the government is a formidable challenge for the knowledge, skills and professional expertise of the medical profession. It is suggested that the problem might be addressed as a physician would address any complex diagnostic and therapeutic patient care problem, using all the knowledge, skills and problem-solving expertise of medicine and, in this case, of medicine as a social discipline.[1] As in any complex case in clinical medicine, this will require working together with the persons involved, other professional disciplines and parties at interest, whether in the public or private sectors, to find a solution, agree upon it, institute it, monitor it and change it when necessary as experience and data accumulate, until a satisfactory solution is eventually in place.

The pendulum will surely swing once more. As the Bible says, "For the poor always ye have with you" (John 12, v 8). Caring for the poor is certain to surface once again as a large problem. Advocacy carries heavy responsibilities. Will the profession be ready with something to advocate when the time comes? There is still some lead time, enough to prepare a thoughtful, workable, proactive response to what will inevitably be another "crisis" in health care.

MSMW

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Amyloid in the Human Brain

THE CLINICOPATHOLOGIC CASE REPORT given in this issue by Filloux and Townsend draws attention to a type of cerebrovascular disease that physicians should be aware of, particularly since, as general experience indicates, the varieties of stroke resulting from hypertension are considerably less frequently seen now than formerly. The illness that Filloux and Townsend have described in their patient is an excellent illustrative example of a form of localized, nonsystemic amyloidosis that affects the cerebral blood vessels and can lead, as they have shown, to intracerebral hemorrhage with a distinctive clinical profile. In their discussion and literature citations, the authors provide an informative review of what is now known regarding this subject.

As they indicate, there clearly is a relationship between the amyloidosis of the cerebral vessel walls and the presence of the scattered foci of amyloid deposition, formerly called senile plaques and now more accurately referred to as neuritic plaques, that are typically seen within the substance of the cerebral cortex in patients with Alzheimer's disease, or senile dementia of the Alzheimer type, in persons of advanced age without dementia and in older patients with Down's syndrome. Briefly stated, patients with cerebrovascular amyloidosis—generally termed cerebral amyloid angiopathy, but also often called congophilic angiopathy because of the characteristic staining of amyloid with Congo red—tend also to have neuritic plaques in the cerebral cortex, whereas patients with Alzheimer's disease and intracortical neuritic amyloid plaques tend also to have cerebral amyloid angiopathy.

The meaning of this association has not yet been entirely clarified, however. Glenner, one of the world's experts on amyloidosis in general, has lately been devoting particular attention to this cerebral form.[1-3] On the basis of his studies of the postmortem findings in a series of 51 cases of well-documented Alzheimer's disease, in which he found cerebral amyloid angiopathy in 92%, he has suggested that the primary event is amyloid formation in the blood vessel walls, which leads in turn to escape of amyloid-forming protein into the substance of the brain, thus giving rise to the plaques.

Not all are in agreement with his hypothesis, however, since others have not been able to find cerebral amyloid angiopathy in as high a proportion of cases of Alzheimer's disease as he has reported.[4] Our own (unpublished) experience in an active neuropathological service in a large general hospital, where Alzheimer's disease is by no means a rare condition, indicates that although there clearly is an overlap between cerebral amyloid angiopathy and intracortical amyloid plaques, they are by no means invariably conjoined; there is a considerable number of cases in which the one form of cerebral amyloidosis is present, while the other is absent. This question is now the subject of intensive research, stimulated by the increasing awareness of Alzheimer's disease as a devastating cerebral disease of major importance. As of the present, however, the pathogenesis of amyloid deposits either in cerebral blood vessels or in the tissues of the brain remains wholly unknown.

As to the amyloid itself, it has long been realized that it is not a single substance. The term was introduced by Rudolf Virchow during his studies of cellular pathology in the middle of the last century; it was based on his demonstration of an amorphous extracellular substance that had staining properties in common with starch or cellulose ("amyloid" = starch-like).[5] The histopathologic literature is replete with discussions as to which of various dyestuffs might provide the best way of identifying and defining amyloid. The most generally acceptable methods now for recognizing it in tissues are by showing that the substance in question is stained with Congo red and, when so stained, gives a yellow-green ("apple green") birefringency under polarized light, and by showing its characteristic fibrillar structure on electron microscopy. As Glenner has shown, these tinctorial and morphologic features of amyloid result when any of various proteins take on the spatial configuration of twisted β-pleated sheet fibrils because of the effect of pathogenetic mechanisms that are only partly understood.[1-3] On the basis of recent studies, Glenner and Wong have suggested that the composition of the amyloid protein isolated from the amyloid fibrils of cerebral amyloid angiopathy in patients with Alzheimer's disease has no homology with any known protein sequence, so that it may be specific for Alzheimer's disease.[6] Masters and colleagues meanwhile have reported the results of studies indicating that the amyloid in the neuritic plaques and that in the vessels in patients with cerebral amyloid angiopathy may have a common origin.[7]

It seems likely that new knowledge as to the precise nature and origin of amyloid in the substance and in the blood vessels of the brain will soon be forthcoming. From a clinical point of view, it seems clear that in spite of overlaps, amyloid deposition in the brain is associated in general with two disparate syndromes—the progressive dementia of Alzheimer's disease (or senile dementia of the Alzheimer type) and Down's syndrome—in which the amyloid takes the form of intracerebral plaques—and cerebrovascular lesions. The cerebrovascular

lesions are usually in the form of lobar hemorrhages that can be multiple and that result from the deposition of amyloid within the walls of small cerebral blood vessels, leading to weakening of the vessel wall and subsequent rupture.

For the sake of completeness, it should be mentioned that there is also a rare form of cerebrovascular amyloidosis that occurs as a dominantly transmitted hereditary disorder in Iceland, unassociated with Alzheimer's disease, which also leads to multiple cerebral lesions. The amyloid protein in this disorder apparently differs from that in the more usual form of cerebral amyloid angiopathy exemplified in the present report.[3] Moreover, what appear to be amyloid plaques in the brain are also seen in the transmissible spongiform encephalopathies—kuru (so far identified only in New Guinea), some cases of Creutzfeldt-Jakob disease and experimentally induced scrapie in animals. Here, likewise, the deposited substance, which has attracted great interest because it may represent aggregates of the infective viruslike agent, appears to be fundamentally different from the far more frequent variety of cerebral amyloidosis that was reported.[3]

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Case Reports

Hematogenous *Pasteurella multocida* Brain Abscess

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Pasteurella multocida, a common cause of infections in animals, is being reported with increasing frequency as a human pathogen.[1] Most infections arise from animal bites and remain localized. More serious deep-seated infections occur occasionally and sometimes involve the central nervous system. There are only five published case reports of brain abscess caused by *P multocida,* all of which were caused by penetrating trauma or contiguous spread from a suppurative parameningeal focus. We describe the case of a patient with a hematogenously acquired brain abscess caused by *P multocida,* apparently the first documented case of this type.

Report of a Case

The patient, a 67-year-old man with mild alcoholic liver disease and severe chronic obstructive pulmonary disease, was admitted to hospital at the Seattle Veterans Administration Medical Center (VAMC) because of a two-day history of headache, sore neck, myalgias, confusion and fever. Before this admission his respiratory illness had necessitated treatment with prednisone, 15 mg a day, continuous supplemental oxygen and bronchodilators. Bronchoscopy and bronchography on three occasions in the past three years for evaluation of a persistent right lower lobe infiltrate on roentgenograms had shown no evidence of malignancy or bronchiectasis. Because of increasingly purulent sputum, he had been receiving ampicillin, 500 mg orally every six hours, for the ten days before hospital admission. The patient had had a pet dog for several years.

On admission the patient's temperature was 40°C (104°F) and his respiratory rate was 28 per minute. Examination of the head, auditory canals and oropharynx disclosed no abnormalities. He had a stiff neck and a positive Kernig's sign. Rales were heard at the right lung base. The findings of cardiac and abdominal examinations were unremarkable and no skin lesions were noted. The patient was confused and lethargic, but the remainder of his neurologic examination showed no abnormalities. The leukocyte count was 30,400 per μl with a predominance of polymorphonuclear cells. A chest x-ray film was unchanged from previous studies. A computed tomographic (CT) scan of the head (without contrast) was normal. Lumbar puncture showed an opening pressure of 285 mm of water and the cerebrospinal fluid specimen contained the following: glucose 80 mg per dl, protein 252 mg per dl, 2,900 leukocytes per μl (80% polymorphonuclear cells) and 11 erythrocytes. Stains and cultures for bacteria, mycobacteria and fungi were negative, as were cryptococcal antigen and counterimmunoelectrophoresis studies. Cultures of urine and blood specimens were sterile; the sputum grew only normal respiratory flora. Following empiric therapy with chloramphenicol, 6 grams given intravenously per day, the patient's fever subsided and he became progressively more alert. On the sixth hospital day a repeat cerebrospinal fluid examination showed only 15 leukocytes (all lymphocytes) and cultures were again negative. Chloramphenicol therapy was discontinued after ten days, and the patient was discharged two weeks after admission, completely recovered neurologically.

Two days after discharge a course of oral ampicillin was begun because of an episode of *Hemophilus influenzae* bronchitis. Five days later he again had headache, stiff neck, fever and progressive confusion. Ten days following his hospital discharge, while en route to the VAMC, he suffered a respiratory arrest. On admission to another hospital he was comatose with a temperature of 40°C (104°F) and a systolic blood pressure of 80 mm of mercury. His neck was rigid and he had unilateral decerebrate posturing. A CT scan of the head showed a 4 by 4 cm right frontal lobe mass and at least four smaller lesions in the right parietal and left and right occipital lobes; all lesions enhanced with contrast (Figure 1). The frontal lobe lesion was drained and a thick abscess wall was removed at craniotomy. Aerobic and anaerobic cultures of an aspirate of the abscess fluid yielded a pure growth of *Pasteurella multocida,* sensitive to all antimicrobials to which it was tested, including ampicillin and chloramphenicol. Blood and urine cultures were negative.

The patient initially received parenteral moxalactam disodium, oxacillin sodium and metronidazole, all of which were later shown to inhibit the *P multocida* isolate. Therapy was changed to penicillin G only, 12 million units given intravenously per day, when the final culture results were known. The patient was transferred to the Seattle VAMC where, after seven days of steady improvement, he became febrile to 39°C (102°F), tachypneic and obtunded. Another CT scan of the head showed four contrast-enhanced lesions, smaller than those seen seven days previously. Repeat cultures of specimens of the cerebrospinal fluid and blood were negative. Antimicrobial therapy was changed to parenteral nafcillin sodium, 12 grams per day, and moxalactam, 8 grams per day, but the patient remained obtunded and intermittently febrile. Another head CT scan ten days after readmission showed eight to ten abscess cavities (Figure 2). A percutaneous needle aspiration of one of the new abscesses produced fluid that showed rare Gram-positive cocci on Gram's stain, but aerobic and anaerobic cultures were negative. Ultrasound examinations of the abdomen and chest and an echocardiogram failed to reveal a source for the brain abscesses. His condition

(Wallace M, Lipsky BA: Hematogenous *Pasteurella multocida* brain abscess. West J Med 1985 Oct; 143:520-523)

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
VAMC = Veterans Administration Medical Center

deteriorated and he died six weeks after his second hospital admission.

On autopsy examination there were three encapsulated brain abscesses. Tissue Gram's stain of these lesions showed rare Gram-positive cocci but cultures were negative. The right middle and lower lobes of the lungs showed chronic and acute inflammation, but no active infection. No abnormalities were noted in the ears, mastoids or paranasal sinuses, and no other source of infection could be identified.

Discussion

Among the *Pasteurella* species, *P multocida* is the most frequent human pathogen. It is a small Gram-negative bacillus that grows well on blood but not MacConkey agar; 16 serotypes have been identified, 6 of which are known to cause infections in humans.[2] *P multocida* is commonly part of the normal respiratory flora of numerous species of mammals and birds.[3] Human respiratory carriage occurs occasionally, usually among healthy people who work with livestock or patients with chronic bronchopulmonary disease who are exposed to household pets harboring the organism.[3,4]

Human disease can be traced to animal exposure in about 75% of all cases[4] but in only about half of those with systemic infections.[3] Patients with chronic pulmonary or liver disease, especially when elderly, seem predisposed to disseminated *P multocida* infections.[5-10] The spectrum of disease caused by this organism includes infected bite wounds, the most common form of infection[3,11-14]; respiratory disease, including bronchitis, pneumonia, bronchiectasis, lung abscess, empyema and paranasal sinusitis,[15-19] and disseminated disease. At least 49 cases of *P multocida* bacteremia have been reported.[20,21]

Central nervous system infections with *Pasteurella* species occur infrequently, constituting less than 5% of non-bite-related cases.[4] Meningitis has been the most commonly reported form, with *P multocida* the predominant species in the 27 documented cases.[20-25] Only five previous cases of brain abscess have been reported, all with *P multocida* as the infecting organism (Table 1).[26-30] Four of these were due to chronic purulent middle ear and mastoid infections, and one resulted from direct cerebral inoculation by a dog bite. Two cases of intracranial subdural empyema caused by *P multocida* have also been reported (Table 1). One of the patients was a man with alcoholism who had metastatic carcinoma of the tongue and in whom *P multocida* bacteremia probably infected a chronic subdural hematoma.[31] The other patient

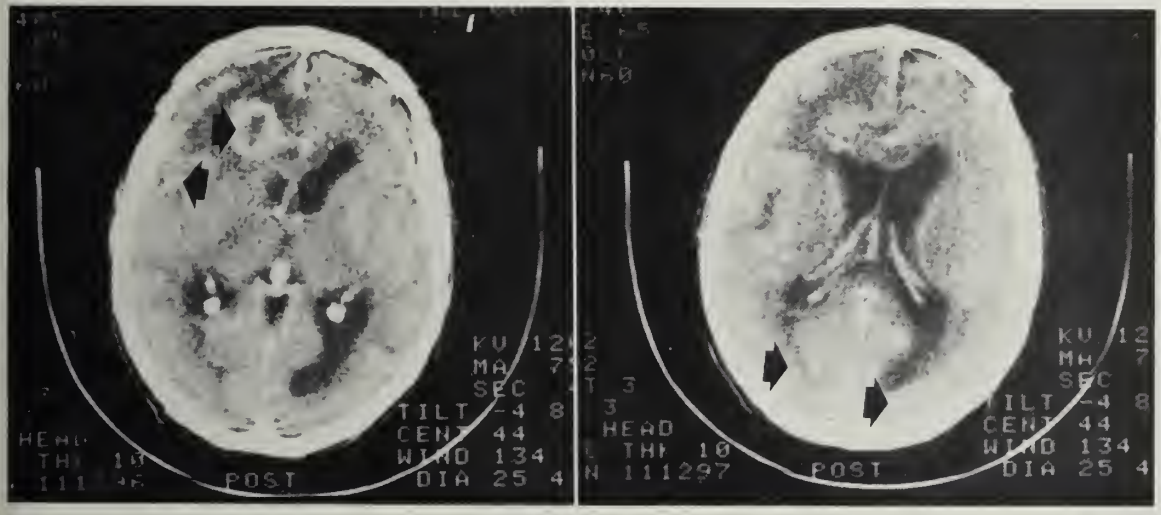

Figure 1.—Computed tomographic scan of the head, with contrast, showing a 4 by 4 cm right frontal lobe abscess and three smaller abscesses **(arrows)**.

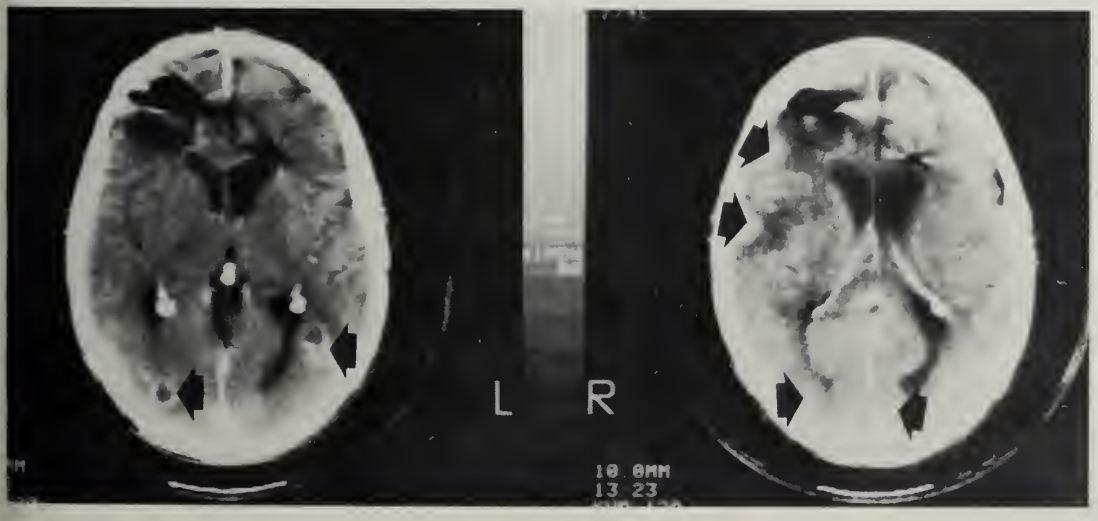

Figure 2.—Computed tomographic scan of the head, with contrast, taken 19 days after Figure 1, showing several of the 8 to 10 abscess cavities **(arrows)**.

had chronic paranasal sinusitis and a subdural empyema developed two weeks after an ethmoid polypectomy.[32,33] In four of the five cases that provided the information, exposure to animals (cats or dogs) was reported. In two cases in addition to ours, Gram-positive cocci were grown from or seen on stains of a specimen of the abscess fluid. *P multocida* grew from other sites (ear drainage, mastoids, pharynx, blood) in four cases and from the responsible animals in two cases. All of the previously reported cases showed a single abscess, unlike in our patient, who had multiple abscesses. Because culture of only one of these lesions was positive, however, the microbial cause of the others is uncertain. All of the patients received both surgical drainage and antibiotics; only two (including our patient) did not recover.

Because most of the cases of meningitis and one of the cases of subdural empyema caused by *P multocida* were presumably hematogenously acquired, it is not surprising that brain abscess with this bacterium could also occur by this route. In our patient the multiple abscesses and the lack of a contiguous source of infection make the bacteremic route likely, despite the absence of positive blood cultures and the failure of extensive premortem and postmortem investigations to identify a primary source. The initial focus was most likely his chronic pulmonary infection. Such infections are common antecedents to hematogenously acquired brain abscesses, and *P multocida* is known to infect patients with chronic bronchopulmonary disease.[4] Alcoholic liver disease, which this patient had, is also recognized as a risk factor for *Pasteurella* septicemia.[6,7,14] The failure to grow the organism from several sputum and blood cultures was likely caused by his receiving antibiotics to which the organism was sensitive before these cultures. Furthermore, a light growth of *P multocida* in a sputum culture with mixed respiratory flora would likely not have been detected. The finding of rare Gram-positive cocci on both premortem and postmortem Gram's stains of abscess fluid may represent either contamination at the time of the original operation or a true second pathogen. While penicillin is the usual drug of choice for *Pasteurella* infections,[34] the atypical course of our patient's illness, the invasive procedures he underwent and his apparent worsening during therapy led to his receiving broad-spectrum antimicrobial therapy. Why he failed to respond to surgical drainage and appropriate antibiotic coverage is unclear, but his severe underlying illnesses and perhaps corticosteroid-induced immunosuppression may have been partly responsible.

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TABLE 1.—*Intracranial Abscesses Caused by* Pasteurella multocida

Sources, Patient Age (yr), Sex	*Site of Infection*	*Predisposing Factors*	*Animal Exposure*	*Cultures*		*Treatment*	*Outcome*
				*CNS**	*Other*		
Brain Abscesses							
Svendsen, 1947[26] 18 ♂	Cerebellum	Mastoiditis	None	Pm and anaerobic streptoccoci	. . .	Penicillin, sulfadiazine; surgical drainage	Recovered
Harris et al, 1953[27] 11 ♀	Cerebellum	Mastoiditis	Cats	Pm—pure growth	Mastoid—pure growth	Penicillin; surgical drainage	Died
Larsen et al, 1969[28] 14 ♀	Cerebellum	Mastoiditis	NA	Pm—GPC seen, not grown	Ear swab—no Pm	Oxacillin sodium, chloramphenicol, sulfadiazine; surgical drainage	Recovered
Klein and Cohen, 1978[29] 1½ ♀	Frontoparietal lobe	Cranial dog bite	Dog	Pm—? pure growth	Dog's mouth—Pm present	"Antibiotic therapy"; surgical drainage	Recovered
Whittle and Besser, 1982[30] 65 ♀	Temporal lobe	Mastoiditis	NA	Pm—pure growth	Ear swab—Pm present	Penicillin, metronidazole; needle aspiration	Recovered
Present case 67 ♂	Frontal, parietal, occipital	Chronic bronchopulmonary disease	Dog	Pm—pure growth; GPC seen, not grown	No Pm isolated elsewhere	Oxacillin, moxalactam disodium, metronidazole; surgical drainage	Died
Subdural Empyemas							
Khan and Chan, 1981[31] 62 ♂	Frontoparietal lobe	Metastatic carcinoma; alcoholism	Dogs	Pm—? pure growth	Blood and pharynx—Pm isolated	Ampicillin; surgical drainage	Recovered
Stern et al, 1981[32]; Ellner and Correa-Londoño, 1981[33] 44 ♀	Frontal lobe	Chronic sinusitis; S/P ethmoid polypectomy	Cats and dogs	Pm—? pure growth	Pets' mouth—Pm present	Penicillin, chloramphenicol; surgical drainage	Recovered

CNS = central nervous system, GPC = Gram-positive cocci, NA = information not available, Pm = *Pasteurella multocida*, S/P = following (status post)

*Specimens for culture were taken from either an intracranial abscess or epidural empyema.

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Rhodamine B Ingestion as a Cause of Fluorescent Red Urine

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RHODAMINE B is a compound with various commercial uses, most notably as a dye. Due to their toxic and carcinogenic potential,[1-4] rhodamine derivatives are not utilized as food additives and their use in cosmetics is restricted by the Food and Drug Administration (FDA). Two cases of rhodamine B ingestion were encountered at the University of California, San Diego (UCSD), Medical Center. Rhodamine B was found in food products allegedly purchased from a bakery in Tijuana, Mexico, and ingestion resulted in urine that fluoresced intensely under long-wave ultraviolet light. A report of human ingestion of rhodamine B has not been previously published.

(Kelner MJ: Rhodamine B ingestion as a cause of fluorescent red urine. West J Med 1985 Oct; 143:523-524)

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Submitted, revised, September 1, 1984.

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Reports of Cases

Case 1

The patient, a 17-year-old man, arrived at UCSD Medical Center complaining of red urine and left flank pain. He stated that he had been "kneed" in wrestling practice earlier that day. He said he had had no previous episodes of colored urine and did not use any drugs. On abdominal examination there were no abnormalities except for mild tenderness over the left iliac crest. The urine was bright red on examination. Both hematuria and myoglobinuria were excluded by laboratory analysis. Further questioning revealed that he had ingested large amounts of red chili peppers and cranberry juice 24 hours earlier. However, the patient had ingested this food combination on numerous occasions without having red urine. A urine specimen was then sent to the Toxicology Laboratory, UCSD Medical Center, for further analysis. There a series of intensely fluorescent compounds was detected by chromatography of the urine. On further investigation we learned that the patient had purchased "pink-colored" cookies from a bakery in Tijuana, Mexico, and had eaten several of them the previous day. The patient's family subsequently provided a cookie for analysis.

Case 2

A 25-year-old woman in her third trimester of pregnancy was admitted to UCSD Medical Center for evaluation of a recent seizure episode. Analysis of a specimen of her urine by the Toxicology Laboratory showed intensely fluorescent compounds. The patient said that she had visited Tijuana earlier in the week and had purchased numerous bakery goods there. However, she could not recall whether any of the goods were pink or red.

Laboratory Analysis

In the Toxicology Laboratory the urine specimens and the cookie showed intense red fluorescence under long-wave ultraviolet light. Thin-layer chromatography for drugs of abuse[5] was done on the urine specimens from case 1 and case 2 and on a methanolic extract of the cookie from case 1. Five fluorescent compounds were noted in each of the urine specimens. Analysis of the cookie extract showed two fluorescent compounds, one of which corresponded to a major compound in the urine using five chromatography systems. Both infrared and ultraviolet-visible spectra for purified commercial rhodamine B and for one of the two compounds found in the cookie were identical. The amount of rhodamine B in the cookie was estimated gravimetrically to be at least 100 mg. Another major compound in the urine had ultraviolet and visible spectra identical to those published for triethylrhodamine, a rhodamine B metabolite.[6,7] The other fluorescent compounds in the urine were conceivably further de-ethylated metabolites of rhodamine B,[4,8] while the other compound in the cookie was either a contaminant or a degradation product of rhodamine.

Discussion

Rhodamine B ("basic violet 10," "food red 15," "FD&C red 19") is used commercially as a dye, fluorescent paint, analytic reagent and a cosmetic coloring agent.[9] The compound has toxic properties and is considered to be a possible carcinogen.[9] Oral administration to mice and rats is

ABBREVIATIONS USED IN TEXT

FDA = Food and Drug Administration
UCSD = University of California, San Diego

reported to cause lymphomas, stomach polyps, growth retardation and death due to hepatic damage.[1,2,4] The compound also has shown mutagenic activity in the Ames test and it causes DNA damage in hamster ovary cells.[3] The use of rhodamine B as a cosmetic additive in the United States is restricted by the FDA. Lipstick cannot contain more than 6% rhodamine B by weight and oral ingestion is limited to 0.75 mg per day.[9] The cookie from case 1 contained more than 130 times this maximum allowed amount. While red urine due to dye or food ingestion is often considered innocuous, the two cases presented here suggest otherwise. The use of food additives in some countries is not as stringently controlled as in the United States.

In neither of the two cases, however, was there any direct evidence to suggest that the symptoms—case 1, flank pain; case 2, seizure—were associated with rhodamine B ingestion. Comparing symptoms with those of previous cases is not possible as this is the first report of human ingestion of rhodamine B. We do not know how widespread is the ingestion of rhodamine B, but the cookies can be easily obtained from bakeries in Tijuana. As to why rhodamine B was used to color bakery goods, one can only speculate. The most likely explanation is its brilliant pink to red color and its fluorescent properties.

Addendum

Since preparation of this manuscript, additional cookies containing rhodamine B were obtained from a store in Tijuana. Apparently this is a continuing problem.

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Treatment of Chronic Myelomonocytic Leukemia

Vincristine and Prednisone Therapy During Symptomatic Phase or After Transformation to Acute Leukemia

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PRIMARY DISORDERS of bone marrow production characterized by varying dysplastic abnormalities have been termed myelodysplastic syndromes. Included among these are refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia.[1,2] Treatment of patients with these disorders has been unsatisfactory, particularly after transformation to a symptomatic phase of disease with or without transformation to acute leukemia. We report here four cases of patients with chronic myelomonocytic leukemia who were symptomatic or whose disorders had changed to acute leukemia and who achieved hematologic remissions after receiving vincristine sulfate and prednisone.

(Taetle R, Haerr R: Treatment of chronic myelomonocytic leukemia—Vincristine and prednisone therapy during symptomatic phase or after transformation to acute leukemia. West J Med 1985 Oct; 143:524-527)

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Methods

Peripheral blood and bone marrow smears were stained with Wright-Giemsa stain according to standard techniques. Histochemical stains were done as previously described.[3] Terminal deoxynucleotidyl transferase (TdT)-positive blood cells were detected using rabbit antibovine TdT (Bethesda Research Laboratories, Gaithersberg, Md),[4] and fluorescence developed with fluorescein-conjugated, goat antirabbit immunoglobulin G. Both positive and negative controls were run with each specimen.

Patient Characteristics and Results of Treatment

The characteristics of four patients seen with chronic myelomonocytic leukemia at the University of California, San Diego (UCSD), Medical Center are summarized in Table 1. All four patients had elevated leukocyte counts and more than 1,000 circulating monocytes per μl. Bone marrows in all patients showed myeloid hyperplasia with varying numbers of monocytes and monocyte precursors. Three patients had palpable spleens. Other supporting laboratory data varied. Patient 1 had bone marrow karyotypic analysis done on three separate occasions, showing only normal metaphases. She underwent marrow transformation to acute leukemia, and histochemical stains were compatible with acute myelomonocytic leukemia. Patient 2 presented with systemic symptoms including fevers, sweats, weight loss and peripheral edema. His serum lactic dehydrogenase (LDH) level was greatly elevated (Table 1), but the peripheral blood differential showed only small numbers of circulating blast cells. Patient 3 also had a transformation of his condition to acute leukemia. Blast

ABBREVIATIONS USED IN TEXT

LDH = lactic dehydrogenase
TdT = terminal deoxynucleotidyl transferase
UCSD = University of California, San Diego

morphology in this patient was consistent with acute monocytic leukemia and a urinary lysozyme level was elevated to 8.1 μg per ml (normal <2.1). TdT was assayed in the peripheral blood of two patients and the bone marrow of a third, and less than 5% positive cells were found.

All patients received therapy with vincristine and prednisone at varying dosages and schedules. Vincristine was given intravenously at doses of 1.0 to 2.0 mg at intervals of one to three weeks. The prednisone dosage varied from 60 to 100 mg a day and was administered for at least five days following vincristine injections. Patient 3 had been previously treated with busulfan, which caused a decrease in his leukocyte count but had no effect on his peripheral cytopenias or organomegaly (Figure 1). In all four patients, the vincristine and prednisone therapy was accompanied by a rapid fall in the circulating leukocyte count, restoration of the leukocyte differential to a normal pattern and abrogation of thrombocytopenia (Figure 1). Variable effects were seen on hemoglobin concentration. In patient 2, systemic symptoms and abnormal chemical values, including LDH and bilirubin, also returned to normal. All three patients with splenomegaly had dramatic reduction in spleen size in response to vincristine and prednisone therapy. In patients 1 and 2 this response was accompanied by resolution of hepatomegaly and patient 3 had dramatic resolution of lymphadenopathy. Representative cases are presented below.

Response durations were 5, 5, 12 and 2+ months, respectively. Toxicity attributed to the drug therapy was minimal. In patient 2, a steroid psychosis developed after his first course of therapy, but he tolerated further therapy at a reduced prednisone dosage without incident. Dosage adjustments in vincristine were required because of symptomatic paresthesias in one patient and elevation of the serum bilirubin level in another.

TABLE 1.—*Characteristics of Patients With Chronic Myelomonocytic Leukemia*

Patient	Age, Sex	Date	Leukocyte Count /μl	Monocytes /μl	Hb grams/dl	Platelet Count /μl	Blasts /μl	TdT	Splenomegaly	LDH U/ml*	Bilirubin mg/ml†
1	59 ♀	3/78 Chronic phase	30,400	1,800	11.1	440,000	0	NT	+1	150	1.8
		8/81 Acute phase	150,000	15,000	8.0	40,000	22,000	NT	+2	440	2.0
2	79 ♂	Chronic phase	19,500	2,700	11.0	37,000	100	Negative	+3	1,500	2.2
3	63 ♂	11/81 Chronic phase	25,600	7,200	13.3	145,000	0	NT	+1	330	1.8
		3/82 Acute phase	194,600	64,000	8.9	70,000	29,100	Negative	+2	500	2.2
4	62 ♀	10/83 Chronic phase	54,000	28,600	3.7	32,000	0	Negative	0	242	0.9

Hb = hemoglobin, LDH = lactic dehydrogenase, NT = not tested, TdT = terminal deoxynucleotidyl transferase

*Normal <180 U/ml.
†Normal <1.5 mg/ml.

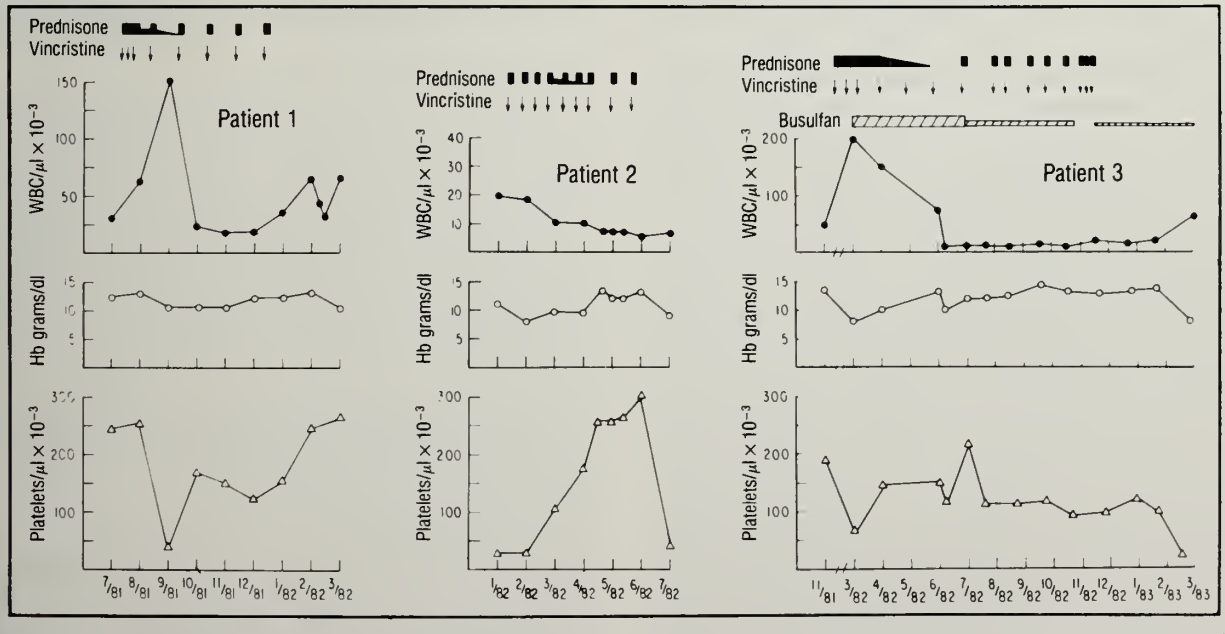

Figure 1.—Effects of vincristine sulfate and prednisone therapy on hematologic values in three patients with chronic myelomonocytic leukemia. WBC = leukocyte count

Reports of Cases

CASE 2. Patient 2, a 79-year-old man, presented in October 1981 to his physician with a two-month history of fatigue, nonproductive cough, fever and night sweats. On physical examination, the patient had 3+ pretibial edema without other signs of congestive heart failure and hepatosplenomegaly. A chest x-ray film was normal. The bone marrow could not be aspirated, but a biopsy specimen showed panmyeloid hyperplasia with abundant megakaryocytes and myeloid forms. Multiple vitamins were prescribed, but the patient's symptoms worsened.

In January 1982 he was seen at the UCSD Medical Center with continued weakness, edema, night sweats and fever. On physical examination, the spleen was palpable 8 cm below the left costal margin and the liver span was enlarged to 18 cm; 2 to 3+ pretibial edema was present. The leukocyte count was 19,500 per μl and the differential 19% polymorphonuclear leukocytes, 7% bands, 1% metamyelocytes, 1% myelocytes, 4% blasts, 15% monocytes, 30% lymphocytes and 23% immature mononuclear cells of uncertain lineage. The LDH level was 1,500 units per ml (normal <180) and total bilirubin 2.2 mg per ml (normal <1.8). A repeat bone marrow study was attempted and again the marrow could not be aspirated. Touch preparations of a biopsy specimen showed erythroid forms with abnormal morphology showing nuclear delay and karyorrhexis. Megakaryocytes were present on the touch preparations and a biopsy specimen, and many showed single, large nuclei. The biopsy specimen showed myeloid hyperplasia with a myeloid-erythroid ratio of 5:1. Reticulin was mildly increased. The patient's peripheral blood contained no TdT-positive cells.

He was treated for one month with a regimen of folic acid, vitamin B_{12} and pyridoxine without response. Treatment with vincristine and prednisone, 60 mg a day (Figure 1), was then begun. The initial dose of vincristine was reduced because of an elevated bilirubin level, but the dose was subsequently 1.5 mg every two to three weeks. The patient experienced a steroid psychosis after five days of prednisone therapy, and this medication was temporarily discontinued. Subsequently he received 40 mg per day of prednisone for five days every two to three weeks and tolerated this well. On this therapy, his leukocyte count returned to normal, his hepatosplenomegaly resolved, his platelet count rose into the normal range and his systemic symptoms abated completely (Figure 1). His edema resolved and his LDH and bilirubin levels returned to normal. He returned to work and remained well until July 1982. Recurrence of systemic symptoms, hepatosplenomegaly and increased LDH and bilirubin values were noted, and his platelet count fell abruptly. He was treated with cytarabine (cytosine arabinoside) without response and died several weeks later. Permission for an autopsy was not obtained.

CASE 4. Patient 4, a 62-year-old woman, presented with a six-week history of anorexia and weakness. She noted a 9-kg (20-lb) weight loss and complained of mild nausea and occasional vomiting. She was referred to the UCSD Medical Center for evaluation. On physicial examination, the patient appeared pale but in no acute distress, without palpable lymph nodes, liver or spleen. The leukocyte count was 54,000 per μl with 19% polymorphonuclear leukocytes, 28% lymphocytes and 53% monocytes. Many of the monocytes were large and had abnormal nuclei with indistinct nucleoli. A subpopulation of the polymorphonuclear leukocytes showed hypersegmentation. The hemoglobin was 3.7 grams per dl and the platelet count 32,000 per μl. A bone marrow biopsy specimen showed a 90% to 95% cellularity with an abnormal number of immature myeloid and monocytic forms. Blasts were less than 5% of the nonerythroid elements. The megakaryocytes showed abnormal morphology; some were small with single, eccentrically placed nuclei and others extremely large with complex nuclei occupying nearly all of the cell. Erythroid precursors showed megaloblastoid maturation and karyorrhexis, but no ringed sideroblasts were present. Immunofluorescent staining for TdT showed no positive marrow cells.

The patient received vincristine, 2 mg given intravenously each week, and prednisone, 60 mg a day, for three weeks. At the end of the first week, her leukocyte count was 1,500 per μl, with 45% polymorphonuclear leukocytes, 51% lymphocytes and 4% monocytes. After transfusion of two units of packed erythrocytes, her hemoglobin was 11.1 grams per dl and the platelet count was 59,000 per μl. After two weeks, her leukocyte count was 8,700 per μl with 27% polymorphonuclear leukocytes, 61% lymphocytes and 12% monocytes. The hemoglobin was 10.9 grams per dl and the platelet count 166,000 per μl. She continues to receive vincristine, 2 mg given intravenously, and prednisone, 60 mg a day for five days every three weeks. Her most recent leukocyte count was 16,300 per μl with a normal differential, her hemoglobin was 10.3 grams per dl and a platelet count was 376,000 per μl.

Discussion

The four cases described in this report conform to previous descriptions of chronic myelomonocytic leukemia.[1,2,5,6] They showed excess proliferation of monocytes and granulocytes, chronic phases of varying duration and hyperplastic bone marrows with ineffective blood cell production in one or more cell lines. Morphologic evidence of dyserythropoiesis, thrombopoiesis or both was present. Two patients had transformation of their disorder to acute monocytic or myelomonocytic leukemia after periods of months to years, a phenomenon well described in cases of chronic myelomonocytic leukemia.[7]

Although descriptions of this disorder,[7] chronic erythromonocytic leukemia,[8] erythromonocytic leukemia[9] and subacute myelomonocytic leukemia [10] have appeared in the past, there have been few reports of effective therapy for these disorders. Various authors have recommended 6-mercaptopurine, methotrexate, hydroxyurea[6] or extremely judicious use of cytarabine or other treatments for acute nonlymphocytic leukemia.[7] Treatment of this rare disorder with any standardized combination chemotherapy regimen has not been reported.

The four patients described here all had dramatic symptomatic improvement and improvement in blood counts after treatment with vincristine and prednisone. Symptomatic remissions were accompanied by regression of organomegaly and normalization of chemical values reflecting organ congestion and ineffective hemopoiesis (LDH). Remissions were seen in two patients with acute leukemic transformations of disease and two symptomatic patients who presented with clinically significant reductions in platelet and erythrocyte counts. Remissions were of short duration (5, 5, 12 and 2+

months, respectively) but contributed substantially to quality of life and were obtained with minimal morbidity.

Previous reports of vincristine-prednisone therapy for cases of monocytic leukemia are difficult to compare with the present series because of changing patterns of treatment of acute leukemia and diagnostic criteria for chronic myelomonocytic leukemia. Geary and co-workers obtained a remission of two years' duration in a symptomatic patient using combinations of cyclophosphamide, vincristine, prednisone, cytarabine, 6-mercaptopurine, thioguanine and daunorubicin hydrochloride.[7] Shaw and Nordquist[11] noted two patients with "pure" monocytic leukemia, one of whom had a "partial remission" and the other a "complete remission" while receiving vincristine and prednisone therapy alone; durations of response were not reported. In our patients, various schedules of administering vincristine and prednisone were used and optimal schedules for drug administration or inclusion of other agents remain undefined. In two patients, symptoms appeared to worsen when intervals between vincristine and prednisone cycles were extended to more than three weeks.

The effectiveness of vincristine and prednisone in a subset of patients with blast transformation of chronic myelocytic leukemia is well documented, and durations of response are similar to those noted in our patients.[12,13] Numerous studies indicate that patients with chronic myelocytic leukemia in transformation whose blast cells contain the enzyme TdT respond to vincristine and prednisone therapy, whereas those whose blasts lack this enzyme seldom respond.[11,12] We did an analysis for TdT in three patients with chronic myelomonocytic leukemia and were unable to show the enzyme in peripheral blood blasts or bone marrow from three patients responsive to the regimen of vincristine and prednisone. Obviously, conclusions regarding the predictive value of TdT in cases of chronic myelomonocytic leukemia cannot be reached using such a small number. These results suggest, however, that TdT may not predict vincristine and prednisone responsiveness in such cases. These drugs provide palliation for symptomatic patients or those with acute blastic transformation. Determining the percent of responsive patients will require larger numbers.

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Minoxidil-Associated Pericarditis and Fatal Cardiac Tamponade

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THE USE OF MINOXIDIL is associated with pericarditis.[1-3] There have been no reports in the literature of hemorrhagic pericarditis caused by minoxidil. We report this case of hemorrhagic pericardial tamponade in a patient receiving minoxidil and heparin to underscore this potential complication.

Report of a Case

The patient, a 70-year-old man with a history of severe hypertension for at least 17 years, had been admitted to hospital in 1971 and 1973 for congestive heart failure attributed to hypertension. Renal insufficiency occurred in the late 1970s with serum creatinine values between 2.5 and 3.5 mg per dl. He never required dialysis. Minoxidil was first used in December 1982 to control his hypertension. His medical regimen at the time of his final admission was furosemide, 40 mg per day; metolazone, 10 mg per day; metoprolol, 25 mg twice a day; clonidine, 0.4 mg twice a day; minoxidil, 10 mg twice a day; nifedipine, 40 mg four times a day; isosorbide dinitrate, 20 mg four times a day; potassium chloride, 40 mEq twice a day, and nitroglycerin sublingually as needed for angina.

His other medical problems included type II diabetes mellitus, hypercholesterolemia and severe diffuse atherosclerotic coronary vascular disease. He had resection of an abdominal aneurysm in February 1981. In June 1982 he had transient right arm and leg weakness for which he refused workup. In January 1983 he experienced a sensory stroke of the right side of the body from which he recovered in one month. An echocardiogram done in April 1983 showed thickened left ventricular walls and a small posterior pericardial effusion. In August 1983 he was admitted because of several hours of sharp left pleuritic chest pain. The pain radiated to the left arm but remained unchanged with different postures. There was no hemoptysis, diaphoresis or nausea.

He appeared apprehensive and in mild distress. Blood pressure was 165/88 mm of mercury with a 15 mm of mercury paradox, pulse was 108 and irregular, respiratory rate 32 and regular and temperature 36.7°C (98°F). Fine rales were present at the lung bases. On cardiac examination he had a 2/6 systolic ejection murmur but no gallop rhythm. No pleural or pericardial rub was appreciated. The jugular venous pressure was estimated at 7 cm of water. An electrocardiogram showed a new onset of atrial fibrillation with a

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ABBREVIATIONS USED IN TEXT

HLA = human leukocyte antigen
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

ventricular response of 110 to 120 beats per minute and more pronounced anterolateral ST-segment depression. Arterial blood gas determinations done while the patient was breathing room air showed pH 7.49, partial oxygen pressure (P_{O_2}) 58 torr and partial carbon dioxide pressure (P_{CO_2}) 29 torr (previous arterial blood gas measurements in April 1983 showed pH 7.41, P_{O_2} 90 torr and P_{CO_2} 36 torr.) A chest x-ray film showed borderline cardiomegaly and platelike atelectasis at the left lung base. A ventilation-perfusion lung scan showed good ventilation throughout both lungs and a segmental perfusion defect in the anterior basal portion of the left lower lobe.

Administration of heparin by continuous infusion was started for presumed pulmonary thromboembolism and activated partial thromboplastin times were maintained at 2.5 times control values. Warfarin therapy was initiated and the prothrombin time was 1.6 times control value at day 6 of his hospital stay. His chest pain abated gradually over three days. His cardiac rhythm converted spontaneously to normal sinus rhythm on day 1 of the hospital admission, but atrial fibrillation recurred on day 5 and intermittently thereafter until his death (two days later). On day 6 hypotension developed, which resolved with saline infusion. The hemoglobin concentration and the electrocardiogram were unchanged. On day 7 he again became hypotensive and the jugular venous pressure was estimated at 8 cm of water. A Swan-Ganz catheter was placed. Initial pressures were as follows: pulmonary wedge pressure, 15 mm of mercury; pulmonary artery diastolic pressure, 15 mm of mercury; right atrial pressure, 7 mm of mercury; cardiac output, 3.5 liters per minute. Pulmonary artery wedge tracings showed a normal X and Y descent. Saline infusion corrected his hypotension temporarily. Repeat hemodynamic measurements were as follows: pulmonary wedge pressure, 20 mm of mercury; pulmonary artery diastolic pressure, 20 mm of mercury; right atrial pressure, 15 mm of mercury; cardiac output, 1.5 liters per minute. Metabolic acidosis and obtundation developed. The Swan-Ganz catheter malfunctioned and was no longer of clinical benefit. Respiratory arrest and intractable ventricular fibrillation occurred soon afterwards and cardiopulmonary resuscitation was unsuccessful. No intracardiac injections were administered.

Postmortem findings were 100 ml of clotted and liquid blood that exited under pressure when the pericardium was incised. The pericardial sac was covered with adherent blood-tinged fibrinous exudate. Microscopically this displayed moderate lymphocytic pericardial infiltration, with a hemorrhagic fibrinous overlay (Figure 1). The 700-gram heart showed pronounced left ventricular hypertrophy and severe coronary arteriosclerosis with 80% occlusion of the anterior descending artery. On microscopic examination there were tiny areas of ischemic myocardial fiber loss without confluent areas of necrosis. Severe arteriosclerotic glomerular loss was evident throughout both kidneys. A patent distal aortic graft was identified. The remaining organs showed only the changes of acute and chronic passive hyperemia.

Figure 1.—Pericardium. A moderate, predominantly lymphocytic infiltrate is present within the pericardial fat as well as the overlying fibrinous exudate (hematoxylin-eosin, reduced from magnification × 350).

Discussion

The association of the use of minoxidil and pericarditis has been recognized during the past decade. Asymptomatic pericardial effusion, symptomatic pericarditis and life-threatening cardiac tamponade have all been reported with its use.[1-3] Although not all observers have agreed on this association,[4] the consensus is that minoxidil can cause pericardial disease.

A patient with renal insufficiency seems to be at particular risk for the development of minoxidil-associated pericarditis. Zarate and co-workers[1] reported an 81% prevalence of pericardial effusion in regularly dialyzed patients as contrasted with a 23% prevalence in a comparable dialysis group not treated with minoxidil. Reichgott[2] reported nine cases of pericarditis associated with minoxidil. All the patients had renal dysfunction at the time pericarditis developed (not all were receiving dialysis). Marquez-Julio and associates[2] prospectively observed that of 18 patients being treated with minoxidil for refractory hypertension, pericardial effusion developed in 7 (39%). Five of these patients had renal impairment. Our patient had renal insufficiency but never required dialysis.

The largest series in which the relation between pericardial disorders and minoxidil was examined is a retrospective review from the Upjohn Company and the University of Massachusetts.[4] The study consisted of a treatment group using open-labeled minoxidil on an experimental protocol for severe hypertension. It contained 477 dialysis patients and 1,392 nondialysis patients. The diagnosis of pericardial disorders was based on reports of adverse reactions, intercurrent medical events and deaths. This most likely underestimated the incidence of pericardial disease. In the dialysis group, 46 pericardial disorders were recognized, 14 with tamponade. The nondialysis group had 45 cases of pericardial disorders, 7 with tamponade. In the nondialysis group 4 of 32 patients with effusion alone had no recognizable risk factor; 2 of the patients with tamponade had no recognizable risk factor. The authors felt that no association was shown between minoxidil and pericarditis. Their conclusion was based on similar incidences of pericardial disease within the dialysis group and historical controls. The design of this study does not lend itself to definitive conclusions. It was also suggested that a 4.5-kg (10-lb) or greater weight gain during minoxidil therapy may be a marker for pericardial disease developing in otherwise risk-free patients. Our patient did not have any weight gain while being treated with minoxidil.

Pathologic descriptions of the features of minoxidil-related pericarditis are available from the literature. Evans and Tucker[5] reported chronic fibrinous pericarditis at autopsy. Houston and colleagues[6] and Webb and Whale[7] described exudative characteristics of a pericardial effusion at pericardiocentesis. Webb and Whale's case of pericardial effusion with a high protein content occurred in a patient with no underlying risk factor. Interestingly, the patient also had a pleural effusion. Human leukocyte antigen (HLA) typing of this patient included B8 and B27 alleles. As the authors discuss, both alleles are associated with autoimmune diseases. There is no report of an analysis of the HLA state of other patients with minoxidil-induced pericarditis. At autopsy our patient had chronic fibrinous pericarditis consistent with previous pathologic findings of minoxidil-related pericarditis.

The common causes of hemopericardium include neoplasm, myocardial and great vessel ruptures into the pericardial sac, trauma, surgical procedures and anticoagulant therapy.[8] In our patient the risk factors for hemopericardium were his anticoagulation and pericarditis. Guberman and co-workers[9] found 11 of 56 medical patients with cardiac tamponade to be anticoagulated in a retrospective review at the University of Cincinnati. Five cases occurred during anticoagulation for acute myocardial infarction and six cases in uremic patients receiving dialysis long term with intermittent anticoagulation. Of the remaining five receiving anticoagulants for various reasons, three were excessively anticoagulated at the time of tamponade. Our patient was not excessively anticoagulated. Blau and associates[10] and Goodman[11] have separately reemphasized the danger of anticoagulation with concomitant pericarditis.

In four autopsy series,[12-15] an incidence of 2% to 4% of hemopericardium associated with cardiopulmonary resuscitation has been reported. None of these series specifically analyzes the risk of hemopericardium in anticoagulated patients during cardiopulmonary resuscitation. Whereas our case might be explained as pericardial bleeding caused by cardiopulmonary resuscitation, this would recognize the pericarditis as only coincidental and ignore the terminal clinical course and hemodynamic variables consistent with but not classical for cardiac tamponade.

This case reemphasizes the difficulty of antemortem recognition of cardiac tamponade, particularly with atypical hemodynamic values, and the danger of anticoagulation in a case of pericarditis. We wish to alert clinicians to the possibility of clinically unrecognized pericarditis in a patient using minoxidil. When such a patient requires anticoagulation, we recommend careful clinical monitoring at the least or consideration of alternative antihypertensive therapy.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Ocular Effects of Gravity Inversion

TO THE EDITOR: In a letter to the editor entitled "More on Gravity Inversion" in the August 1984 issue,[1] Goldman and colleagues conclude that oscillating about a horizontal axis during gravity inversion instead of hanging statically is a safe activity and specifically poses no risk to the eyes. They allude to different results in a new study and they state that "the hydrostatic increase in intraocular and central retinal artery pressure balance and protect each other. . . . Each prevents the other from damage." Unfortunately, this conclusion is unsupported by facts.

In the original study that Goldman co-authored,[2] he and his colleagues determined that the intraocular pressure (IOP) increased 84% from an average of 19 to 35 mm of mercury after three minutes of static inversion and suggested that because of the significant elevation of IOP, visual fields and tonometry be carried out before embarking on an inversion program. In the "new" work that was alluded to in the letter and now published,[3] he and his associates reported that with oscillation IOP rose from a preinversion level of 17 to 33, 32 and 31 mm of mercury at 5, 10 and 15 minutes, respectively. The net increases were thus 94%, 88% and 82%, depending upon the duration of inversion. The "new" IOP results are virtually identical with those found in their earlier study; yet, despite this fact, Goldman and associates reach completely different conclusions and now declare that inversion with oscillation is safe. I find this a most peculiar turn of events.

My ophthalmologist colleagues and I have investigated many of the ocular effects of gravity inversion.[4-6] We recently have evaluted optic nerve function in normal subjects during inversion and have demonstrated significant depressions of the amplitude of visual signals conducted from the eyes to the occipital cortex (pattern reversal visual evoked potentials) and have also demonstrated visual field defects. These alterations in function, although they disappear upon returning to the upright position, are undoubtedly related to the intraocular pressure rise during inversion and are found also in patients with glaucoma without inversion. Hence, the statement that the body completely compensates for the intraocular pressure rise during inversion activities by increasing perfusion is mere fantasy with respect to these functional tests.

It remains uncertain whether healthy persons who use gravity inversion equipment for short daily intervals over several years will suffer any permanent damage from increased IOP. Nevertheless, enthusiasts of inversion ought to at least be informed of the potential risk to the eyes, although it may be limited. Furthermore, this risk can probably be reduced by decreasing the inversion times to short 10 or 15 minute intervals. Since elevated IOP is usually asymptomatic, the authors' previous suggestion[2] that potential inversion devotees at least have an initial baseline intraocular pressure measurement to determine if they are at special risk is appropriate. This seems a more prudent and responsible approach than to come to a totally different conclusion, based on essentially unchanged data and mere speculation, as the authors did in their letter.

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* * *

Dr Goldman Replies

TO THE EDITOR: Thank you for the opportunity to respond to Dr Friberg's comments. I think some points should be clarified. When we published the first study ever to examine the physiologic effects of static inversion (utilizing gravity inversion boots) several years ago, we were at first alarmed at our findings, as we did not expect to see such dramatic elevations in intraocular pressure (IOP), central retinal arterial and systemic blood pressure.[1] Upon further examination we attempted to note responses to other forms and techniques of inversion (compared with vigorous exercise levels,[2] in hypertensives[3] and oscillating[4,5]). Throughout all our studies we have always stressed that all participants undergo a cardiovascular and ocular examination.

We were, however, dismayed by the sensationalized media coverage of our papers and other research papers proclaiming that this type of adjunct training was not safe for anyone. We then set out to find if oscillating techniques would afford any variance from our original data in a pilot study. As Dr Friberg so astutely pointed out, our data in the mentioned pilot study[4] (later performed with well-trained subjects) were

similar to static inversion results, but he chose to ignore the significant subjective responses of the subjects recorded in the questioned article, and systemic blood pressure and pulse rate readings. As mentioned, we found the subjects not to experience the "headaches, nausea, head congestion, dizziness—while experiencing a calm, relaxed feeling of well being and tranquility." Please note that in our original studies subjects were inverted for only 3 minutes statically, versus 15 minutes of oscillation in this study. This, of course, is not hard statistical data but aided us in developing a manner in which the oscillating devices may differ from static hanging boots with a stationary bar.

Our reference to aerospace studies[6] was an attempt to discern why we have not as yet noted in the medical literature cases of stroke, cardiovascular incidents or eye injury in normal persons in the nearly two decades these devices have been popular. There have been some sparse reports of periorbital petechiae and transient engorgement of the scleral capillaries, but mostly those were in untrained persons subjected to prolonged periods of static hanging or anticoagulants (or both) in almost subtle attempts to induce side effects. In one study we were sent to review, the researchers inverted subjects statically for three 10-minute periods in a row following administration of aspirin.

We agree with Dr Friberg and colleagues that there may be some long-term effects associated with inversion; however, we think in addition to evaluations of potential glaucoma associations, energies might also well be spent on discerning how to invert and for what time period for maximum safety.

IOPs should be tested on a regular basis should glaucoma be a concern, but we have already stressed this numerous times. I believe if one were able to measure the above mentioned parameters on some centrifugal rides at amusement parks or during deep sea diving, the results might bring this issue into better perspective.

We recommend that persons who wish to invert use an oscillating device and do not stay in the inverted (−90 degree) posture for more than a few seconds, while heeding their own body responses, and for no more than 15 minutes. Please note again that although the data were similar, the device utilized was quite different and the subject population was one trained in inversion, and their subjective experiences were significantly different from those in previous studies.

Perhaps future work will better outline guidelines for use of intermittent traction with inversion devices, but we feel that compared with many other forms of adjunct athletic training, inversion should not stand apart from such activities as powerlifting, scuba diving or plyometrics. There are risks inherent in all, but before condemning the modality I would like to see more documented statistical data reporting cases of ocular injury in healthy people (those without hypertension or glaucoma tendencies) who utilize inversion in the manner we outline.

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Medi-Cal Reimbursement System

TO THE EDITOR: The news media report Medi-Cal (California's medicaid program) fraud from time to time. Periodically, some provider bills for services never performed and gets caught. This is relatively trivial fraud but should be prosecuted. The significant Medi-Cal fraud, however, is that perpetrated upon Medi-Cal providers. No doctor who cares for Medi-Cal patients is immune to ripoff.

The doctor who renders care in good faith and then bills Computer Sciences Corporation (CSC) may never get paid. The claim may not be done precisely as CSC wishes it done. If this is the case, there will be a request for more or correct information. Even when the missing information is supplied, there is no assurance of reimbursement. If the diagnosis is cancer and there are two office visits in one month, for example, one visit will be paid at about half the usual and customary charge and the other visit will not be paid at all. If a patient is seen many times in one month in an effort to avoid admission to hospital, the state will save two ways: no hospital costs and disallowed office visits.

My personal litany of CSC experiences is long even though I care for few Medi-Cal patients, all of whom are sick. Obtaining Medi-Cal reimbursement actually is possible. The first thing to do when shortchanged by CSC is to send to that computerized bureaucracy a "Claims Inquiry," a form that is amazingly (for CSC) simple. CSC has no motivation at all to be sympathetic and unless there is a compelling reason, such as a mistake on their part, the "Claims Inquiry" may go nowhere. Don't stop there.

Although there is no motivation on the part of CSC to please the doctor, a letter to CSC from my assemblyman works wonders. For example, the claim for a patient with intractable pain who had to be seen at least once a week suddenly became valid.

Every California doctor has an assemblyperson. When all else fails, turn your Medi-Cal reimbursement problems over to her or him. There is no need to be embarrassed by doing so. Our legislators need to be made aware that the Medi-Cal reimbursement system isn't working. They and you will benefit.

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On the 'Blackness' and 'Whiteness' of Patients

TO THE EDITOR: Like so many articles on osteoporosis and hypertension, the conference on estrogen[1] for postmenopausal women in the May issue differentiates black people from whites. I have long believed that this differentiation is

not valid in America because so many blacks obviously have varying admixtures of "white blood." I don't believe any researcher ever questions "black patients" along these lines: "Were your parents and grandparents and great-grandparents completely black?" "How can you be sure there is no white blood in your lineage?" Are white patients similarly asked, "How can you be sure there is no black blood in your ancestors?" Furthermore, I have read that thousands of very light-skinned blacks "pass" each year into white society. Are we sure they are never classified as white patients? So how can any research article on racial differences be valid?

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Physicians as Financial Scapegoats

To the Editor: The study by Brown and colleagues on Medi-Cal (California's medicaid program) hospital contracting in the July issue was timely and interesting. The conclusion seemed to be that this system achieved "its legislative objectives." No mention is made of medical diagnosis and treatment which should be the substance of medicine. Hospitals are the process and, like "health care," have been institutionalized. This sounds as if the thesis of Illich in *Medical Nemesis* has been confirmed.

From where I and any reasonably observant person sits, it is apparent that the hospitals are making out. But what about the physician and surgeon services? Who is making up the deficits incurred by Medi-Cal payments of some 18% to 20% of a standard fee?

Expenses are expenses. Medical and hospital supply houses have not cut their fees 80%, nor have pharmaceutical companies, office equipment manufacturers and suppliers, accountants, medical books and journals, hotels, airlines or automobile companies. I also have noted no reductions in mandatory CME course fees, legal fees or concomitant malpractice insurance premiums.

What is happening here is a continuing squeeze on professional service budgets, particularly in full-time physician academic centers, and most assuredly affecting those who are associated with contract hospitals that are referred major trauma cases as emergencies. The time-honored solution to make up for the deficits incurred by the untenable state professional financing schemes is to raise the fees to private charge patients. The result is progressive alienation of the middle and upper economic class—that is, the majority.

It would be interesting to examine the details of why the hospitals at the University of California, Irvine and Davis, were reported to have something like a $26 million loss and needed an emergency bailout from the legislature. More needs to be frankly reported and the public and the boards of trustees who are charged with the fiduciary responsibility of our hospitals need to be informed. The story seems fragmented and the thinking fuzzy. Who was responsible for accepting the unsound federal and state cost reimbursement methods of financing hospital care before the ax fell with DRGs and medical contracting by the Medi-Cal "Czar"?[2]

Regarding costs, physicians apparently enjoy their role as *bouc emmissaire* (scapegoats). We want to uphold our tradition of altruism and our perceived image as mendicant friars, but the secular society in which we live would have to have the same image for this to work. There is no evidence that it does.

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A Physician's Dual Responsibility in Disability—To Patients and to Society

To the Editor: A physician's primary responsibility is to his or her patient but there is a secondary responsibility because physicians' recommendations have a major impact on disability costs. Poor health is one of the few acceptable excuses (if not the only one) for not working in our society and sick leave is frequently abused. DRGs have mandated shorter hospital stays and technological advances allow earlier hospital discharge; yet, in many cases, patients are off work longer.

Employees have gradually become used to greater and greater periods of time off. Employers recognize their role in this problem and are instituting controls into the system but they need the support of physicians. Clinical judgment usually suffices for determining the amount of time a patient needs to recuperate and the Minnesota Medical Association has published a temporary disability duration guide.[1] The presidents of the San Diego County Medical Society and the San Diego Employer's Health Cost Coalition[2] have signed a joint letter to members of the physician community reminding them of their role in unnecessary sick leave.

Patients should not have an extra week or two off just because they have sick time left. Patients who are seen in the office on Tuesday and are able to return to work should be released for work on Wednesday and not for the following Monday. An astute physician finds out what the patient actually does at work and ascertains whether a modified assignment is a reasonable option (it may also help the patient return to full-pay status). A common trap is for the physician to verify disability after the fact and become an enabler in the abuse of sick leave.

A prominent example of a rapid convalescence is the recent illness of President Reagan. Everyone would agree that his was a major surgical procedure; however, this 74-year-old patient began assuming some of his duties 10 to 14 days after the operation. It is hard to sanction the often-lengthy convalescence of many 30- or 40-year-old patients—those who seem to require six to eight, and sometimes ten, weeks before they can resume employment following an elective surgical procedure.

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High-Risk Surgical Procedures

To the Editor: A surgical procedure may be cancelled because of high-risk status. Is it high risk because of the patient's medical complications, lack of facilities in an institution or variable operator skill?

The following illustrates what can be done at an above-average hospital with good anesthesia control. Success has to be the result of working together and necessary consultations before the operation. The patient's hysterectomy had already been cancelled at another hospital when her blood pressure had spiked to 210/100 mm of mercury in the operating room.

Report of a Case

The patient is 63 years old, obese, gravida 6 and postmenopausal for 14 years with a complaint of three months of vaginal bleeding. She also has urinary stress incontinence necessitating wearing a pad every day for several years. The procedure required is a dilatation and curettage and likely vaginal hysterectomy, bilateral salpingo-oophorectomy and anterior and posterior repair.

Our problem is she also suffers from episodes of atrial fibrillation and transient ischemic attacks (strokes) that leave her face or arm numb for hours to days. A Bioscan shows a small soft ulcerative plaque in her right carotid artery. She is diabetic and requires both methyldopa and a diuretic for hypertension. She has a hiatal hernia and frequent urinary tract infections. She has only one kidney. She is a confirmed Jehovah's Witness and will not accept blood under any circumstances. She has been taking 11 medications a day: tolazamide (Tolinase), naproxen, codeine with acetaminophen (Tylenol), propranolol hydrochloride (Inderal), digoxin, cimetidine, methyldopa, hydrochlorothiazide with triamterene (Dyazide), dipyridamole, aspirin and calcium lactate.

With preoperative evaluation; consultation with a cardiologist, internist and anesthesiologist, and careful counseling with family members about possible adverse outcome, surgical procedures can be completed for patients with multiple medical complications. In the above case, a fractional dilatation and curettage was carried out, followed a week later by vaginal hysterectomy, left salpingo-oophorectomy and anterior and posterior colporrhaphy. There was no damage to her bladder. Blood pressure remained below 160/80 mm of mercury and blood loss was less than 200 ml. On the day after the operation she was ambulatory and returned home on the fourth day. Credit has to be given to good team work and preoperative preparation.

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Topics in Primary Care Medicine

Pharyngitis

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J McPHEE, MD
Series' Editors

Although most persons with pharyngitis do not consult physicians, sore throat is one of the most common reasons for office visits. The challenge is to define the subgroup of patients who merit more than nonspecific symptomatic treatment.

Two interrelated management questions should be considered: Should a throat culture be carried out? Should an antibiotic be prescribed?

The answer to these questions depends on the goal of the proposed therapy. In the past, concern about the prevention of rheumatic fever has been the main impetus for the antibiotic treatment of pharyngitis. Other goals are symptom relief, prevention of suppurative complications and prevention of disease transmission. This article will discuss the approach to streptococcal pharyngitis and briefly consider the treatment of other, nonviral causes of pharyngitis, such as gonorrhea or *Mycoplasma*.

Prevention of Rheumatic Fever

In the early 1950s, penicillin treatment of group A streptococcal pharyngitis was shown to prevent initial and recurrent attacks of rheumatic fever. For this reason, the American Heart Association in the past recommended that all patients complaining of sore throat receive a throat culture. If the culture was positive, antibiotics could be given. Waiting several days for culture results before treating was shown not to interfere with rheumatic fever prevention.

Rheumatic fever and its sequelae were once significant causes of debility and death among children and young adults in the United States. But over the last 30 years the attack rate of rheumatic fever has dramatically declined. In most areas of the country, the incidence rate is no more than one to two cases per 100,000 population per year. Indeed, when medical records of patients with rheumatic fever are reviewed, as in Rhode Island, most had either an asymptomatic infection or did not consult a physician despite symptoms. Although children and young adults of lower socioeconomic status from urban areas in the continental United States are felt to be at greater risk, the incidence of rheumatic fever has also declined in many of these areas. For example, the incidence of rheumatic fever among inner city black children in Memphis is fewer than four cases per 100,000. In other areas of the world and in a few areas of the United States, acute rheumatic fever and rheumatic heart disease remain important clinical problems. For example, among Samoan children on the main Hawaiian island of Oahu, the incidence of rheumatic fever is close to 100 cases per 100,000.

The explanation for the decline of rheumatic fever is not known. The downward trend began well before the introduction of penicillin, but widespread antibiotic therapy may have played an additional role. Other factors may be changes in the ecology of the streptococcal organism and improved living and nutritional standards.

For most patients in the United States now, the risks of preventing rheumatic fever by antibiotic treatment of streptococcal pharyngitis approximate the risks of acquiring rheumatic fever. There is a 1 in 200 chance that a patient receiving penicillin will have a drug reaction and a 2 in 100,000 chance of fatal anaphylaxis.

By contrast, group A streptococcal pharyngitis remains a common disease. Of 21,150 throat cultures done between December 1980 and February 1981 by the Rhode Island Department of Health, 17% were positive. The largest percentage of positives were in children and young adults.

Streptococcal Pharyngitis

Common but not specific features of streptococcal pharyngitis are sudden onset of sore throat, accompanied by fever, malaise and headache. In children, there may be nausea, vomiting and abdominal pain. Physical findings may include pronounced inflammation of the throat and tonsils, a discrete patchy exudate and anterior cervical adenopathy. Conditions

(Steinbrook R: Pharyngitis [Topics in Primary Care Medicine]. West J Med 1985 Oct; 143:534-536)

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that may be associated with streptococcal pharyngitis include scarlet fever and acute glomerulonephritis. Other signs and symptoms, such as conjunctivitis, cough, diarrhea, nasal discharge, hoarseness, stomatitis and bullous myringitis, are unusual and suggest another cause of pharyngitis.

Exudative pharyngitis can be caused by other conditions, including viral infections. Persistent systemic illness, lymphadenopathy and splenomegaly suggest the diagnosis of infectious mononucleosis. Diphtheria is uncommon but still occurs in unvaccinated populations. It is characterized by a grey membrane that is firmly adherent to the tonsillar or pharyngeal mucosa.

Streptococcal Throat Cultures

Throat cultures for streptococci in some laboratories cost as much as $20. They utilize a blood agar plate, with neomycin and nalidixic acid added. Colonies which show β-hemolysis are identified as group A or non-group A by disk tests, fluorescent antibody staining or latex agglutination. Non-group A streptococci can cause clinically significant pharyngitis, but not rheumatic fever.

A positive throat culture for group A β-hemolytic streptococci may reflect infection with or asymptomatic carriage of streptococci in the oropharynx. In children the streptococcal carriage rate may be as high as 15%. In one study approximately half of children with pharyngitis were infected and half were carriers. The false-negative rate of a single throat culture in infected patients is about 10%.

The concept of "prior probability"—the likelihood a patient will have a streptococcal infection based on the history and physical examination findings—is helpful in assessing the value of a throat culture. As the prior probability of streptococcal infection increases, the culture becomes less valuable because the results may have little effect upon therapy. Similarly, as the prior probability of infection decreases, the culture becomes less valuable because a positive culture likely represents a carrier state unrelated to the pharyngitis. The culture is most valuable in guiding therapy when the prior probability of infection is intermediate.

The carrier state does not appear to be a significant risk factor for the development of clinical pharyngitis or rheumatic heart disease, except in patients with prior rheumatic fever. Nor is it a significant risk factor for disease transmission. Indeed, patients who cannot be "cured" of oropharyngeal streptococci with repeated courses of antibiotics are most likely to be chronic streptococcal carriers, not acutely infected persons.

Few medical authorities have adopted a "no culture" approach to patients with acute pharyngitis. The reasons for this include the tremendous publicity given to rheumatic fever prevention programs, public expectations about the care of sore throat and the difficulty of distinguishing viral from streptococcal infections by clinical examination. Seeking medical attention for a throat culture may also be helpful in excluding suppurative complications and in providing reassurance and symptomatic relief.

The American Heart Association revised its recommendations for throat cultures in 1984. Throat cultures are said to be "valuable" for children and adolescents and "not as essential" for older patients. They are indicated primarily to avoid the unnecessary use of antibiotics for the 70% to 80% of adults with viral or other types of pharyngitis. Follow-up throat cultures, according to the new recommendations, are not indicated unless the patient remains symptomatic. Cultures of asymptomatic family members and contacts should be reserved for special circumstances, such as in the family of a patient with a history of rheumatic fever or in an epidemic.

New Rapid Diagnostic Tests for Streptococci

Rapid diagnostic tests, involving direct identification of group A streptococci from throat swabs using fluorescent antibody staining, latex agglutination tests or an enzyme-linked immunosorbent assay, are an alternative to a throat culture. There is an expanding number of such tests, which can be carried out in an office setting. The cost of materials is about $2 a test and results can be obtained in less than two hours.

Published reports indicate test sensitivities of 77% to 95% (compared with throat cultures) and test specificities of 86% to 100%. Cases missed are primarily those of streptococcal carriers, who tend to have lower colony counts. There is probably little significance to missing these carriers. The advantages of these tests are rapid diagnosis, less expense, immediate patient knowledge and reassurance, and avoidance of unnecessary antibiotics. The disadvantages include their lack of sensitivity, the time required to do the test and maintain quality control and the need for more time to confirm their reliability. To date, no one of these new tests is substantially more sensitive or more specific than another.

Treatment of Streptococcal Pharyngitis

Children over the age of 3 and young adults with a combination of sore throat, exudative pharyngitis, temperature greater than 37.8°C (100°F) and anterior cervical adenopathy have a significant chance—probably greater than 40%—of streptococcal infection. While viral pharyngitis could also produce these clinical features, the physician should consider empiric antibiotic therapy. Such treatment probably decreases the chance of suppurative complications such as painful adenopathy and peritonsillar abscess. A throat culture is not necessary in most cases because it would not influence the management strategy. Effective antibiotic regimens are penicillin V, 250 mg given orally three or four times a day for ten days, or benzathine penicillin G, 1.2 million units given intramuscularly. For a patient with penicillin allergy, erythromycin, 250 mg four times a day for ten days, is suggested. Cephalosporins are also effective, but are more expensive. Oral treatment is safer than intramuscular therapy. An injection is preferred only if poor compliance is anticipated, a rheumatic person is in the family or in the rare clinical settings where rheumatic fever is more likely. Prevention of recurrent attacks of rheumatic fever in patients with a history of the disease is a separate topic beyond the scope of this article.

Patients with a sore throat but no other features of streptococcal pharyngitis are unlikely—have less than a 5% chance—to have the disease. A throat culture is not necessary. Patients with sore throat and one or two features, such as temperature, exudate or adenopathy, have an intermediate chance. A throat culture may be useful to avoid unnecessary antibiotic use and provide reassurance to the patient.

Symptomatic Relief of Pharyngitis

Streptococcal pharyngitis is a self-limited disease usually lasting less than five days. Several studies from the 1950s suggest that if patients are treated with antibiotics within 24 hours of the onset of symptoms the duration of symptoms *may* be decreased by 12 to 24 hours. Recently, a small, prospective, double-blind study showed a significant symptomatic response of children to penicillin initiated within 72 hours of the onset of streptococcal pharyngitis, compared with placebo. It will be important to learn if this finding is confirmed in other patient groups.

The use of antibiotics for relief of symptoms in patients unlikely to have streptococcal pharyngitis or another bacterial cause of pharyngitis should be discouraged. Over-the-counter lozenges, saline gargles, aspirin or a mild narcotic for severe pain may be efficacious. Patients who smoke should be encouraged to stop.

Physician Practices

Recent evidence suggests that there may be excessive throat culturing and antibiotic use for patients who complain of sore throat. This conclusion is based on the results of a survey in 1981 of the culturing and prescribing patterns of all active primary care physicians in Rhode Island. About half the physicians surveyed obtained a throat culture on all patients with sore throat, regardless of clinical features or therapeutic plan. Close to 90% said they provided antibiotic therapy before culture results were obtained and only 60% stopped the antibiotics if the culture was negative. Nearly half said they often did not receive culture results in time to influence therapy. Two of five physicians obtained follow-up throat cultures after the completion of therapy. This survey suggests that much progress is necessary to achieve a goal of selective culturing and antibiotic treatment, as now recommended by the American Heart Association. Further, this selective strategy offers an opportunity to both reduce the costs of medical care and avoid unnecessary antibiotic use.

Gonococcal Pharyngitis

Gonococcal pharyngitis may occur in sexually active populations. It is particularly prevalent among gay men. The symptoms are usually very mild, with infrequent tonsillar or cervical node enlargement or tonsillar exudate. There may be evidence of gonorrhea at other sites or of disseminated infection.

A careful sexual history is necessary to determine those patients at risk for pharyngeal gonorrhea. There is controversy about the role of pretreatment and follow-up throat cultures. There are limited data and no large randomized trials of therapy. Recommended antibiotics include tetracycline (500 mg given orally four times a day for seven days), procaine penicillin (2.4 million units intramuscularly in each buttock after probenecid, 1 gram orally) or trimethoprim-sulfamethoxazole (nine single-strength—80 mg/400 mg—tablets orally each day for five days). Administering spectinomycin hydrochloride is ineffective.

Chlamydial and *Mycoplasma* Pharyngitis

Clinicians are now focusing attention on other potentially treatable causes of pharyngitis. In a study of 763 adults with sore throat seen in four general medical practices in New England, Komaroff and his colleagues found serologic evidence of infection with *Chlamydia trachomatis* in 20.5% and with *Mycoplasma pneumoniae* in 10.6%. Only 9.1% of patients had positive cultures for group A β-hemolytic streptococci; 17.7% had viral infections and 2% were heterophile-positive. Significantly, no pathogenic organism was identified for many patients. It will be important to confirm these findings in other patient groups.

The study did not address the value of treatment. Based upon its findings, however, erythromycin, to which group A β-hemolytic streptococci, *Mycoplasma* and *Chlamydia* are sensitive, would seem a reasonable antibiotic choice in patients with persistent pharyngitis or in other circumstances leading to empiric therapy.

Summary

Patients at high risk for streptococcal pharyngitis or its suppurative complications should receive antibiotic treatment without throat cultures. Such patients usually have sore throat, fever, anterior cervical adenopathy and pharyngeal exudate. Patients with sore throat and no fever, adenopathy or exudate are unlikely to have streptococcal pharyngitis. They should usually receive symptomatic treatment only. Intermediate-risk patients should receive throat cultures; antibiotics should be withheld until culture results are known. Further research is needed to assess the value of penicillin treatment for symptomatic relief of such patients. Follow-up cultures and routine cultures without symptoms are rarely indicated. Gonococcal pharyngitis should be considered in persons at risk. Finally, some patients may have pharyngitis secondary to *Chlamydia* or *Mycoplasma*. Erythromycin may be effective in treating these patients.

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The Hospital Role of Family Physicians

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This paper examines the hospital role of a random sample of all general and family physicians in the state of Washington. Of the 287 physicians in our sample, 81% admitted at least one patient to hospital during the two-week study period, and the average physician admitted six patients. The majority of the admitting diagnoses fell within the realm of internal medicine. Residency-trained and board-certified respondents were more likely to admit patients to hospital, and residency-trained and rural practitioners were much less likely to refer patients to other physicians for hospital care than their urban counterparts. Residency-trained physicians, in particular, were much more likely to practice hospital obstetrics than those without formal residency training.

These data demonstrate the broad and significant hospital role of the family physician. Given the increased scope and intensity of hospital practice of residency-trained family physicians, and barring major changes in admitting privileges or new regulatory constraints, we predict that this group of physicians will continue to have a significant inpatient role in the United States.

(Rosenblatt RA, Moscovice IS: The hospital role of family physicians [Health Care Delivery]. West J Med 1985 Oct; 143:537-540)

Family practice is a discipline in rapid flux. In 1931 general practitioners constituted 83% of all physicians.[1] By 1967 that percentage had declined to 21% and general practice appeared to be slated for extinction.[2] Only the initiation of approved residency training in family medicine—the lineal descendant of general practice in the United States—prevented the total disappearance of this type of medical practitioner.

In 1980, for the first time in 50 years, the number of American physicians who considered themselves to be general or family physicians increased.[3] At present, 13% of graduating medical students enter accredited programs in family medicine.[4] In 1980 general and family physicians accounted for a third of all ambulatory visits—an amount that was threefold more than the contribution of any other specialty to ambulatory care.[5] Family physicians care for a wider spectrum of the population and are the most frequent source of ambulatory care for all age groups except children under age 17.[6]

But family practice is not just an ambulatory care specialty. General practitioners in the United States have traditionally been active in the inpatient setting, and the average family physician spends about a quarter of his or her professional time in the hospital setting.[7] Despite the importance of inpatient care, the optimal hospital role of the family physician is controversial. The increasing complexity of inpatient medical care has restricted the domain of the generalist, and in certain parts of the country there have been attempts to exclude family physicians from portions of hospital practice.[8] The appropriate role of family practitioners is the subject of ongoing debate, the resolution of which will have a profound impact on how the discipline is defined and the role it plays in American medicine.

The purpose of this study is to examine the content of the hospital practices of general and family physicians in one state. Family practice is an office-based discipline, but the majority of family physicians take care of hospital patients. In an earlier article we studied the determinants of hospital admission rates of family physicians and documented the discretionary nature of the decision to admit patients.[9] This study examines in detail a random sample of all general and family physicians in the state of Washington in an attempt to determine the diagnoses of the patients they admit to hospital and the spectrum of diagnostic entities for which they assume responsibility in the hospital.

Methods

The universe from which the sample was drawn consisted of all professionally active, office-based general practitioners and family physicians in the state of Washington as defined by the American Medical Association (AMA) masterfile. These criteria were met by 1,001 physicians in January 1978—17% of all active physicians in the state. Of these physicians, 394

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were randomly selected for the study and 287 participated, yielding a response rate of 72.8%. Respondents did not differ significantly from the sample universe on the basis of age, sex, US citizenship or residency training; the sample studied did include a significantly greater proportion of physicians who were board certified or located in rural parts of the state, or both.

Each physician studied was contacted first by letter and subsequently by phone and asked to participate in a study of patterns of hospital admissions. The phone interviews were conducted by a trained interviewer and consisted of a verification that the physician met the study criteria and a brief series of questions about the scope of the physician's practice, the number of years the physician had been in his or her current practice and the list of hospitals where the physician admitted patients.

Primary data were collected through the use of two patient logs that were maintained by the physician's receptionist or nurse, an ambulatory patient log and a hospital admission log. The ambulatory log recorded the number of patients by age and sex encountered by the physician in the outpatient setting during two-week study intervals spread throughout 1979 to eliminate seasonal bias. The hospital admission log recorded data about every admission *initiated* by the physician during the study period and included the following information: (1) patient's age; (2) patient's sex; (3) patient's place of residence; (4) primary admitting diagnosis assigned at time of hospital admission; (5) primary source of payment for hospital care; (6) name and location of the hospital to which the patient was admitted; (7) whether the patient was cared for by the admitting physician or was referred to another physician for hospital care; (8) if referred, the specialty of the physician providing the hospital care.

The primary data were supplemented with three types of secondary data:

- The AMA masterfile provided information about the physician's background and training.
- The Area Resource File of the United States Department of Health and Human Services, combined with information from the Center for Health Statistics of the Washington State Department of Social and Health Services, provided demographic and health services data for the counties of Washington State where the physicians worked.
- The American Hospital Association's Guide to the Health Care Field provided information about the characteristics of the hospitals in Washington State to which our physician sample admitted patients.

All the hospital admission data were reviewed on receipt by the senior author and any ambiguities immediately resolved by calling the admitting physician. The primary admitting diagnoses were coded by a certified medical records librarian using the *International Classification of Diseases, 9th Edition* (ICD-9) system. Because the ICD classification system contains thousands of individual rubrics, diagnoses were grouped into 92 distinct diagnostic clusters that bring together conditions that have essentially similar pathophysiologic characteristics or that call for similar clinical responses on the part of physicians; this technique has been described in detail in other publications.[10,11]

In order to further examine the spectrum of diagnoses with which family physicians dealt in the hospital setting, we further grouped the diagnostic clusters into skill domains. A skill domain was defined as that group of diagnoses that traditionally falls within the domain of a particular specialty. Skill domains provide a summary of the composition of the hospital practice of a primary care physician and can be determined using admitting diagnoses. Six skill domains were created for this study: internal medicine, surgery, obstetrics, orthopedics, psychiatry and pediatrics. Table 1 illustrates the concept of skill domains by listing the most frequent diagnostic clusters that fell within each of these categories in this study. The pediatric group differs from the rest in that it is defined as all admissions of children 16 years old and younger, rather than by diagnosis.

Every diagnostic cluster was assigned to one and only one skill domain. The majority of the diagnoses could be easily categorized; diagnostic clusters that might fall within the domain of more than one specialist were assigned to the most likely category by a panel of primary care physicians and specialists. It was possible to successfully classify 98% of the 1,661 hospital admissions initiated by our sample of physicians.

TABLE 1.—*Construction of Skill Domains: Examples of the Diagnostic Clusters Incorporated in Each Domain*

Skill Domain	*Diagnostic Cluster*
Internal Medicine	Malignant neoplasm
	Pneumonia
	Myocardial infarction
	Cerebrovascular accident
	Cardiac arrhythmia
	Chest pain
	Ischemic heart disease
	Diabetes mellitus
	Congestive heart failure
	Diarrheal disease
	Chronic obstructive pulmonary disease
	Urinary tract infection
Surgery	Inguinal hernia
	Head injury
	Appendicitis
	Abnormal menstrual bleeding
	Gastrointestinal obstruction
	Tonsillectomy
Obstetrics	Normal pregnancy
	Complicated delivery
Nonsurgical Orthopedics	Back pain
	Fractures/dislocations
Psychiatric	Anxiety/depression
	Alcoholism
Pediatrics (all admissions younger than 16 years of age)	Pneumonia
	Tonsillectomy
	Abdominal pain
	Diarrheal disease
	Head injury
	Appendicitis
	Upper respiratory tract infection
	Inguinal hernia
	Bronchitis
	Poisoning

Results

Hospital Admitting Patterns

Of the physicians who participated in this study, 94.4% were men, with an average age of 51 years. Some 42% were board certified, but only 12% had completed family practice residency training. There were 38% in solo practice, with 42% located in rural areas, using standard census designations of nonmetropolitan areas to determine rural location.

Of the 287 physicians in our sample, 87.8% admitted at least one patient to hospital during the two-week study interval. The average physician admitted 3.2% of all patients seen during the study, approximately three patients per week. Of the 1,661 patients admitted to hospital by the physicians in our sample, 12.7% were referred directly to another physician who assumed responsibility for the hospital portion of their care. Excluding those patients who were referred to other physicians for hospital care, 80.8% of the physicians in our sample admitted and provided hospital care for at least one patient during a randomly selected two-week period.

In all, 97.0% of all residency-trained and 95.0% of all board-certified family physicians cared for at least one patient in hospital during the two-week study period. Physicians without formal postgraduate training or board certification, by contrast, were slightly less likely to admit a patient to hospital during a two-week interval, a difference that was statistically significant. However, most physicians in all categories maintain a hospital practice. Practice configuration and rural or urban location had little impact on the proportion of family physicians who admitted at least one patient during the study period.

The list of the admitting diagnoses for this sample of physicians is shown in Table 2 and is quite similar to the hospital diagnoses of a national sample of family physicians reported elsewhere.[7] The single most common admitting diagnosis was normal pregnancy (9.9% of all admissions), followed by malignant neoplasm (4.4%), pneumonia (3.8%) and myocardial infarction (3.4%). Most of the patients were assigned a primary admitting diagnosis within the internal medicine skill domain, as shown in Figure 1.

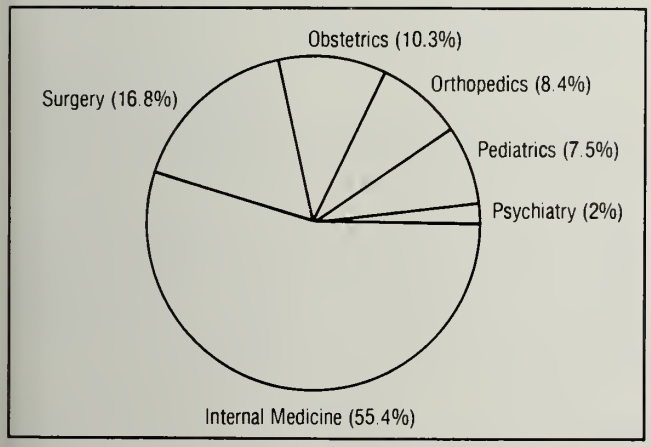

Figure 1.—Proportion of patients admitted to hospital with diagnoses in six skill domains (N = 1,621 admissions). Forty patients could not be assigned to a skill domain and are excluded from this analysis.

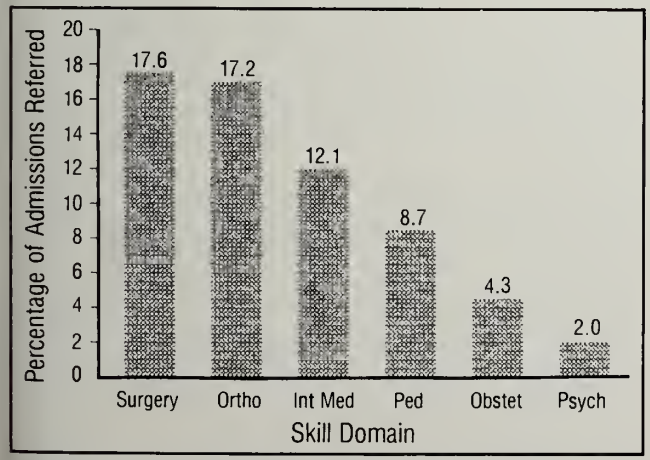

Figure 2.—Percentage of patients referred to other physicians for hospital care by skill domain (N = 1,621 hospital admissions).

Referral Rates

As noted above, 12.7% of hospital admissions initiated by the physicians in our sample were referred directly to some other physician for the hospital portion of their care. The referral rate differed considerably from one skill domain to another, with referral of 17.6% of patients with surgical diagnoses as compared with a 2% referral rate for patients with psychiatric diagnoses as shown in Figure 2. Most referrals were to internal medicine subspecialists (33.5%) and general surgeons (32%). The balance of patients were referred to surgical subspecialists (19.2%), general internists (4.4%), pediatricians (1%), psychiatrists (1%) and other family physicians (5.4%); the specialty of the physician accepting the referral was not recorded in 3.5% of the cases. Referral rates for individual diagnoses varied considerably, ranging from

TABLE 2.—*Most Frequent Primary Admitting Diagnoses for Washington State General and Family Physicians (287 physicians, 1,621 admissions)*

Rank	Diagnosis	Frequency N	Frequency %
1	Normal pregnancy	164	9.9
2	Malignant neoplasm	73	4.4
3	Pneumonia	63	3.8
4	Myocardial infarction	56	3.4
5	Cerebrovascular accident	52	3.1
6	Cardiac arrhythmia	45	2.7
7	Abdominal pain	44	2.7
8	Back pain/radiculopathy	43	2.6
9	Inguinal hernia	39	2.4
10	Fractures and dislocations (other than femur)	37	2.2
11	Chest pain	36	2.2
12	Ischemic heart disease	32	1.9
13	Diabetes	28	1.7
14	Congestive heart failure	27	1.6
15	Fracture of femur	26	1.6
16	Head injury	26	1.6
17	Anxiety/depression	25	1.5
18	Diarrheal disease	24	1.4
19	Chronic obstructive pulmonary disease	21	1.3
20	Appendicitis/appendectomy	20	1.2
21	Abnormal menstrual bleeding	17	1.0
22	Alcoholism	17	1.0
23	Gastrointestinal obstruction	17	1.0
24	Urinary tract infection	16	1.0
25	Peptic ulcer disease	16	1.0

50% for patients with the diagnosis of cholecystitis to no referrals for patients with the diagnosis of urinary tract infection.

Referral rates differed greatly between rural and urban physicians and between those who had taken a formal residency in family medicine and those who were not residency trained. Residency-trained physicians practicing in rural areas referred only 1.9% of the patients they admitted to hospital, as compared with a 22.6% referral rate for urban physicians without residency training, a difference that is statistically significant.

Skill Domains

The percentage of physicians who admitted at least one patient to hospital in each of the skill domains varied from 75.3% for internal medicine to 13.2% for psychiatry. Urban-rural differences were quite pronounced for almost all the skill domains, as seen in Figure 3. Rural general and family physicians are much more likely than their urban counterparts to admit their patients in all areas except internal medicine, where the rates are similar. Residency-trained physicians differed most from the nonresidency-trained group in their involvement with hospital obstetrics. Of the residency-trained physicians, 54.5% admitted at least one obstetric patient during the course of the study, as compared with 23.2% of the group without formal postgraduate training.

Discussion

What is the appropriate hospital role of family physicians? Traditionally, general practitioners and family physicians have maintained active hospital practices in the United States, in contrast to the much more limited hospital role of general practitioners in countries such as Britain.[12] Although there have been concerns about the future availability of hospital privileges for family physicians, surveys have shown that most family physicians are able to receive privileges for a broad spectrum of clinical activities.[13]

The structure of medical practice is changing rapidly. Hospital use is being constrained as third-party payers limit reimbursement for hospital care. Managed health care systems, and in particular capitated health insurance schemes, depend for their efficacy on the willingness of primary care physicians to act as gatekeepers, further constraining hospital use. Those patients who are admitted to hospital are sicker and require more sophisticated technological interventions than in earlier times. Although generalists have been active in hospitals in the past, it is possible that the changing nature of the hospital environment will limit their ability to provide care in the future. On the other hand, the reimbursement system may reward those physicians who are able to provide vertical continuity of care, following their patients from the outpatient to the inpatient environment, and being parsimonious in their use of resources in both settings.

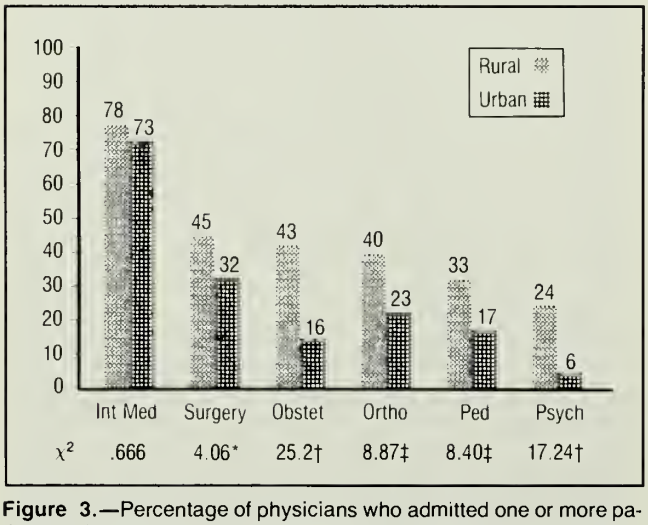

Figure 3.—Percentage of physicians who admitted one or more patients to hospital in each skill domain by practice location. *$P<.05$, †$P<.001$, ‡$P<.01$

This study provides some insight into the clinical content of the hospital practices of family physicians. Because it is a study of the hospital activity of a large random sample of all the family physicians in one state, it provides us with a window through which to observe this portion of the generalist's medical practice. It is clear from this study that family physicians during this study period were quite active in hospitals, with the typical physician admitting three patients per week, and only about 20% of the respondents admitting no patients under their care during a two-week period. Because we received data only on a two-week practice segment from each physician, these figures understate the hospital activity of family physicians. Most family physicians in Washington State maintain a hospital practice.

Residency training is associated with major differences in the hospital role of physicians, with residency-trained physicians about twice as likely to practice obstetrics and less likely to refer patients to other physicians when admitting a patient to hospital. Although this may be partially related to the younger age of residency-trained physicians, this group does appear to have a broader scope of both outpatient and inpatient practice. To the extent that residency-trained family physicians in Washington State represent the future of this discipline, hospital practice will remain an important component of the clinical repertoire of family practice.

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Computer-Assisted Assessment of Family Physicians' Knowledge About Cancer Screening Guidelines

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The understanding and correct application of cancer screening guidelines is an important aspect of early cancer detection. Prior reports have indicated deficiencies in physicians' knowledge of the subject, prompting various educational activities aimed at primary care physicians. By using an interactive computer program to assess knowledge of the American Cancer Society cancer screening guidelines in a group of 306 family physicians, we found that knowledge of this subject continues to leave room for improvement.

(Groveman HD, Ganiats TG, Klauber MR, et al: Computer-assisted assessment of family physicians' knowledge about cancer screening guidelines [Health Care Delivery]. West J Med 1985 Oct; 143:541-544)

The American Cancer Society (ACS) estimates that of the 450,000 Americans who died of cancer in 1984, about 148,000 could have been saved by earlier diagnosis and prompt treatment.[1] Hence, an important aspect of cancer control lies in the application of currently available cancer screening and preventive measures to a larger segment of the general population.

Family physicians have a unique opportunity to provide accurate patient education information and to do the procedures necessary to effect an early diagnosis.[2] In 1980, therefore, the ACS published guidelines for the cancer-related checkup that reviewed their recommendations for screening for the four major internal cancers: breast, cervix, colon and lung.[3] The stated goal of the ACS is that "since the burden of prevention and early detection of cancer rests primarily on the doctor who first sees the patient, the Society's professional education program is particularly directed to the primary care physician."[4]

In an effort to determine the effectiveness of this strategy, the ACS studied primary care physician knowledge about cancer screening guidelines and found that 80% of California physicians reported not being exposed to ACS materials or programs.[5] In a similar ACS report, a study of 35 residents in a family practice residency program showed that 64% of the residents had never been involved in educational activities specifically dealing with cancer prevention and detection and that few residents could correctly state or apply the guidelines.[6]

We describe current knowledge of a group of family physicians about cancer screening guidelines and test the efficacy of the microcomputer in knowledge assessment and interactive teaching. The microcomputer was felt to be ideally suited for assessing physician knowledge because of the considerable interest in this technology, ease of keyboard use, personalized interactive teaching style and response storage capabilities.[7]

Methods

As a volunteer project under the auspices of the California Division of the American Cancer Society, the two physician-authors programmed a 20-minute computer-assisted cancer screening questionnaire and instructional program for the Apple IIe computer. The program contained questions related to physician age, sex and board certification and included 11 questions regarding the ACS guidelines for the cancer-related checkup. Questions were of the multiple choice, true-false and fill-in-the-blank type. A "menu" was used so that physicians could select from one to all four of the course sections: breast, cervix, colon and lung. The program included an optional tutorial on the use of the computer keyboard. Graphics, sound effects and positive reinforcement were used to make the interaction pleasant and entertaining. Following each phy-

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sician response, interactive instruction was tailored to the accuracy of that response. On one of the cervix section questions, a second interrogation was designed to test the efficacy of the computer in facilitating short-term knowledge retention.

To ensure that the program included key concepts primary care physicians should know, the content of the program was reviewed and approved by the Professional Education Subcommittee of the California Division of the American Cancer Society. Each question was presented on two occasions to a group of five physicians during diskette development and minor modifications were made to question content and format to improve the clarity and reliability of the questionnaire. The program was then presented to family physicians as a scientific exhibit at a meeting of the California Academy of Family Physicians held November 9 to 11, 1983, in San Francisco. Twelve computers were made available during the three-day convention to maximize physician participation. Physician responses were stored on diskette for later analyses.

The association between test performance and various factors (age, sex, board certification, need for keyboard review) was tested using the Mantel-Haenszel χ^2 procedure corrected for continuity.[8] Age was stratified in three groups: 21 to 40 years, 41 to 60 years and over 60 years. *P* values were derived from χ^2s in each factor-course table using the 5% level for statistical significance.

Results

A total of 306 family physicians participated by interacting with the computer on at least one of the four sections of the program: 68% took all four, 7% took three, 11% took two and 13% took only one. The course sections were nearly equally popular (Table 1).

Age was directly related to whether a physician requested a computer-assisted tutorial on the use of the computer keyboard (Table 2). Need for keyboard review was independent of board certification, sex and overall test performance.

Overall test scores (for four sections combined) were not significantly correlated to age, sex or board certification (see Table 3). Analysis of data for the individual course sections showed that board certification and sex were unrelated to section performance. Age, however, was significantly correlated on the lung and colon sections, with older physicians doing less well (see Table 4).

In cervix question C-2 (see below), second interrogation scores were tabulated for those physicians who initially gave an incorrect response and who then received interactive computer-assisted instruction on the subject matter. Correct responses were attained in 97% of repeat responders to this question.

Data related to performance in each of the test sections are presented in Table 5.

Breast Cancer

Although 90% of responders correctly answered that fine-needle aspiration or biopsy was necessary in patients with a suspicious breast mass and a negative mammogram (question B-2), only 55% correctly answered concerning the guidelines that a mammogram should be done as a baseline in asymptomatic women between the ages of 35 and 40 years, every one to two years between the ages of 40 and 50 years and yearly thereafter (question B-1). Of responders, 23% would have incorrectly delayed dye- or needle-guided biopsy in the case of a "suspicious area on screening mammogram, but with a normal physical examination" (question B-3).

Cervix Cancer

Only 40% of responders recognized that the American Cancer Society guideline "Pap smears every three years after two negative exams a year apart" was based on all three of the following factors: (1) the time for transformation of carcinoma in situ to invasive carcinoma of the cervix is 8 to 30 years; (2) of women who have had at least one negative Pap test, only 1 in 50,000 women screened will have invasive

TABLE 1.—*Number and Percentage of Family Physicians Participating in the Cancer Screening Guidelines Test by Course Section*

Course	Physicians	
	Number	%
Breast	254	83
Cervix	251	82
Colon	249	81
Lung	256	84
Any course	306	100

TABLE 2.—*Percentage of Physicians, by Age Group, Requesting Computer-Assisted Keyboard Tutorial*

Age Years	Physicians	
	Number	%
21-40	117	52.1
41-60	119	63.9
>60	70	85.7

$P < .001$

TABLE 3.—*Relationship of Total Score to Various Factors*

Factor	Mantel-Haenszel	
	χ^2	P
Keyboard review	0.15	>.5
Age	1.15	.33
Sex	0.27	>.5
Board certification	2.42	.12

TABLE 4.—*Statistical Significance* of Association of Factors With Section Scores*

Section		Factor		
		Age	Sex	Board Certification
Breast	χ^2	0.08	0.88	1.45
	(P)	(.93)	(.35)	(.23)
Cervix	χ^2	2.57	0.53	2.72
	(P)	(.11)	(.47)	(.10)
Colon	χ^2	10.09	0.82	0.68
	(P)	(.0015)	(.36)	(.42)
Lung	χ^2	5.29	0.00	0.65
	(P)	(.021)	(1.00)	(.42)

*One degree of freedom Mantel-Haenszel χ^2 and *P* value.

cancer, and (3) there is a definite regression rate from carcinoma in situ back to normal that one can take advantage of by screening less frequently (question C-1).

In all, 63% of responders understood that the ACS guidelines called for Pap smears only until age 65 (question C-2).

Colon Cancer

Of responders, 57% were aware that if colon cancer was detected early (Duke's stage A), the five-year survival rate exceeds 80% (question CR-1). However, 95% of respondents correctly answered that the ACS guidelines included digital rectal examination, occult blood testing and sigmoidoscopy as screening tests (question CR-3); 93% of responders understood that the sigmoidoscope was still a useful screening tool, even though the location of colorectal cancer had seemingly been moving "higher in the bowel" (question CR-2).

Lung Cancer

Only 23% or responders were able to identify that the five-year survival for a detected lung cancer, even with screening chest roentgenogram and careful history, remained 8% (question L-1). A total of 60% of responders incorrectly felt that there was "no harm" in obtaining screening chest roentgenograms and cytologic analysis of sputum specimens in patients who desired the tests and could afford them (question L-2). In all, 81% of responders correctly identified that the key to preventing lung cancer was to stop smoking cigarettes (question L-3).

Discussion

This study shows that family physicians' knowledge of American Cancer Society screening guidelines varies. Indeed, on more than half of the test questions, less than 65% of responses were correct. Board certification, age and sex had no significant effect on overall test scores, but older physicians did less well on the lung and colon sections.

Knowledge of mammography guidelines was marginal for both men and women physicians, which seems surprising considering recent media attention concerning this procedure. Physicians were also much more inclined to do a biopsy in the clinical setting of a "suspicious mass on physical exam, but with negative mammogram" (90%) than they were to do a biopsy in the setting of a "suspicious mammogram with negative physical exam" (77%). Apparently 23% of the physicians relied so heavily on the physical examination that they would disregard the suspicious findings on a mammogram. The Breast Cancer Detection Project clearly has shown that mammography is the most accurate single examination for breast cancer detection. Indeed, of the 3,557 breast cancers detected in that study, 41.6% were detected by mammogram alone.[9]

Also noteworthy was the percentage of responders (60%) who felt that there would be "no harm" in doing screening chest roentgenograms and cytologic studies of sputum in patients who desired the tests and could afford them. These studies are not recommended as screening tests for high-risk groups because of the high rate of false-positive results (up to 10%), which can lead to invasive procedures such as bronchoscopy and thoracotomy; in addition, screening with chest roentgenogram and cytology has not been shown to improve the outcome in patients with lung cancer.[3]

Age was directly related to whether a physician required a keyboard lesson in the use of the computer. Younger physicians were much less likely to require a review, possibly indicating they are more familiar with computer technology or have already been exposed to the use of a computer keyboard. However, that overall performance was independent of the need for a keyboard review suggests that proficiency in the use of the keyboard was readily gained by those (including older physicians) who completed the computer-assisted tutorial.

The computer was shown to be a valuable teaching aid for acquiring short-term knowledge when one looks at the data for second interrogation on question C-2. Initial correct re-

TABLE 5.—*Number of Participants and Percentage Correct by Question*

Section Correct Answers		Percentage Correct %
Breast (N = 254)		
B-1	Age-related guidelines for mammography (see text)	55
B-2	If a suspicious mass is found but mammogram is negative, aspiration or biopsy should be done	90
B-3	If mammogram is suspicious but exam is negative, next step would be dye or needle-guided biopsy	77
Cervix (N = 251)		
C-1	Rationale for Pap smears every 3 years after two negative smears a year apart (see text)	40
C-2	Pap smears are only recommended until age 65 if exams have been negative previously	63
Colon (N = 249)		
CR-1	Survival rate for a patient with a cancer detected early (Duke's stage A) is greater than 80%	57
CR-2	Sigmoidoscopy is still a useful screening test even though cancers have been moving "higher in the bowel"	93
CR-3	ACS asymptomatic screening protocol (see text)	95
Lung (N = 256)		
L-1	Survival rate for a patient with a detected lung cancer (if screening CXR and sputum cytologies had been done every 6 months) is the same as if no screening had been used (8%)	23
L-2	CXR and sputum cytology do have the risk of leading to more invasive tests and are not recommended for screening	40
L-3	For lung cancer prevention, the physician should recommend smoking cessation	81

ACS = American Cancer Society, CXR = chest x-ray study

sponses were 63% to this question, but after interactive instruction, 97% of those who initially answered incorrectly were able to give a correct response on a second interrogation.

Two possibilities may explain the deficiency in cancer screening guideline knowledge. The American Cancer Society may have been ineffective in disseminating the information concerning the application of their guidelines, or physicians may have been exposed to these guidelines in the past but have rejected them and therefore do not recall their specifics. It is the authors' opinion that the former is the major factor operating. The data presented here are consistent with other studies on the subject.[5,6]

Possible implications of the study would be (1) that family practice residency programs review the adequacy of the cancer curriculum presented during residency; (2) that family physicians in practice might review current patient education and preventive measures in their practices, and (3) that large funding agencies such as the American Cancer Society consider enhancing or redirecting their professional education programs toward primary care physicians.

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In Memoriam

California Medical Association

AXLER, GUERI, Inglewood. Died July 10, 1985, aged 63. Graduate of American University of Beirut School of Medicine, 1947. Licensed in California in 1955. Dr Axler was a member of the Los Angeles County Medical Associaion.

❦

BRANDT, JUSTIN, Woodland Hills. Died February 23, 1985, aged 64. Graduate of State University of New York College of Medicine at New York City, 1950. Licensed in California in 1956. Dr Brandt was a member of the Los Angeles County Medical Association.

❦

COHN, SAMUEL, San Francisco. Died June 15, 1985, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr Cohn was a retired member of the San Francisco Medical Society.

❦

CULBERTSON, JOHN A., La Verne. Died February 5, 1985, aged 75. Graduate of Vanderbilt University School of Medicine, Nashville, 1936. Licensed in California in 1946. Dr Culbertson was a member of the Los Angeles County Medical Association.

❦

FISCHER, WALTER R., Anaheim. Died July 8, 1985, in Anaheim, aged 56. Graduate of Loyola University of Chicago, Stritch School of Medicine, Chicago, 1956. Licensed in California in 1957. Dr Fischer was a member of the Orange County Medical Association.

❦

GREEN, DAVID L., Jr, Stockton. Died September 1, 1984, aged 59.Graduate of the University of California Medical School, Berkeley-San Francisco, 1949. Licensed in California in 1949. Dr Green was a member of the San Joaquin County Medical Society.

❦

HARROUN, PHYLLIS, Oakland. Died June 15, 1985, in Berkeley, aged 82. Graduate of the University of California Medical School, Berkeley-San Francisco, 1929. Licensed in California in 1929. Dr Harroun was a retired member of the Alameda-Contra Costa Medical Association.

❦

HEIDBREDER, GERALD A., San Diego. Died January 21, 1985, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr Heidbreder was a retired member of the Los Angeles County Medical Association.

❦

KEIPP, JAMES V., Long Beach. Died October 25, 1984, aged 72. Graduate of Northwestern University Medical School, Chicago, 1937. Licensed in California in 1937. Dr Keipp was a retired member of the Los Angeles County Medical Association.

❦

KYDDSON, THOMAS W., Sacramento. Died June 15, 1985, in Sacramento, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Dr Kyddson was a retired member of the Sacramento-El Dorado Medical Society.

LARKEY, JEFFERSON, Pebble Beach. Died February 14, 1985, aged 85. Graduate of Harvard Medical School, Boston, 1926. Licensed in California in 1929. Dr Larkey was a retired member of the Alameda-Contra Costa Medical Association.

❦

MARSH, WILLIAM E., Berkeley. Died June 27, 1985, in Walnut Creek, aged 73. Graduate of McGill University Faculty of Medicine, Montreal, 1937. Licensed in California in 1938. Dr Marsh was a retired member of the Alameda-Contra Costa Medical Association.

❦

PRICE, SIDNEY, Sherman Oaks. Died January 22, 1985, aged 77. Graduate of the University at Chicago Health Sciences Center, 1932. Licensed in California in 1946. Dr Price was a retired member of the Sacramento-El Dorado Medical Society.

❦

RAFFERTY, RACHEL P. SHARP, Campbell. Died April 2, 1985, aged 88. Graduate of the Medical College of Pennsylvania, Philadelphia, 1921. Licensed in California in 1922. Dr Rafferty was a retired member of the Santa Clara County Medical Society.

❦

RILEY, BENNET J., Concord. Died January 16, 1985, aged 68. Graduate of Tufts University School of Medicine, Boston, 1952. Licensed in California in 1955. Dr Riley was a member of the Alameda-Contra Costa Medical Association.

❦

SIMONS, JESSE E., Fresno. Died October 4, 1984, aged 63. Graduate of the University of Utah College of Medicine, Salt Lake City, 1950. Licensed in California in 1955. Dr Simons was a member of the Fresno-Madera Medical Society.

❦

SWARTOUT, HUBERT O., Glendora. Died February 1, 1985, aged 96. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1933. Dr Swartout was a retired member of the San Luis Obispo County Medical Society.

❦

YOUNG, CHARLES O., Visalia. Died March 17, 1985, aged 81. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1940. Dr Young was a member of the Tulare County Medical Society.

❦

New Mexico Medical Society

JOHNSON, GEORGE A., Albuquerque. Died May 25, 1985, in Santa Fe, aged 52. Graduate of Baylor University College of Medicine, Houston, 1956. Licensed in New Mexico in 1982. Dr Johnson was a member of the Albuquerque & Bernalillo County Medical Society.

❦

LANE, MARK H., Albuquerque. Died August 7, 1985, in Albuquerque, aged 60. Graduate of the University of Vermont College of Medicine, Burlington, 1954. Licensed in New Mexico in 1967. Dr Lane was a member of the Albuquerque & Bernalillo County Medical Society.

ROWE, FRANK A., Albuquerque. Died August 6, 1985, in Albuquerque, aged 69. Graduate of St Louis University School of Medicine, 1943. Licensed in New Mexico in 1947. Dr Rowe was a member of the Albuquerque & Bernalillo County Medical Society.

Utah State Medical Association

DILLON, WILLIAM H., Salt Lake City. Died July 16, 1985, in Salt Lake City, aged 61. Graduate of Western Reserve University School of Medicine, Cleveland, 1950. Licensed in Utah in 1957. Dr Dillon was a member of the Salt Lake County Medical Society.

Washington State Medical Association

BLACK, JOHN J., Spokane. Died May 25, 1985, aged 76. Graduate of St Louis University School of Medicine, 1934. Licensed in Washington in 1940. Dr Black was a retired member of the Spokane County Medical Society.

BUEHLER, PETER K., Issaquah. Died in November 1984, aged 40. Graduate of the University of Rochester School of Medicine and Dentistry, Rochester, NY, 1970. Dr Buehler was a member of the King County Medical Society.

COLE, JOHN R., Spokane. Died May 24, 1985, aged 66. Graduate of St Louis University School of Medicine, 1943. Licensed in Washington in 1949. Dr Cole was a member of the Spokane County Medical Society.

MORAIN, SACIDE S., Tacoma. Died July 26, 1985, in Tacoma, aged 57. Graduate of University Istanbul Medical Faculty, 1951. Licensed in Washington in 1961. Dr Morain was a retired member of the Pierce County Medical Society.

SMITH, RALPH L., Port Orchard. Died July 19, 1985, in Port Orchard, aged 75. Graduate of the University of Oregon Medical School, Portland, 1939. Licensed in Washington in 1940. Dr Smith was a retired member of the Kitsap County Medical Society.

WATKINS, HARRY C., Jr., Aberdeen. Died April 30, 1985, in Grays Harbor, aged 79. Graduate of the University of Oregon Medical School, Portland, 1930. Licensed in Washington in 1931. Dr Watkins was a retired member of the Grays Harbor County Medical Society.

Wyoming Medical Society

SOMMERS, W. RAY, Casper. Died July, 25, 1985, in Casper of mesothelioma, aged 45. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1972. Licensed in Wyoming in 1977. Dr Sommers was a member of the Natrona County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

THE CIGARETTE UNDERWORLD—Edited by Alan Blum, MD, Editor, *New York State Journal of Medicine*. Lyle Stuart Inc, 120 Enterprise Avenue, Secaucus, NJ 07094, 1985. 128 pages, $9.95.

Cigarette smoking is generally acknowledged as the most important cause of preventable disease, disability and premature death in the industrialized world. The volume *The Cigarette Underworld* is an important source of information on this problem. It first appeared as a special issue (December 1983) of the *New York State Journal of Medicine*. Dr Alan Blum serves as the editor of the *NYSJM*.

Dr Blum assembled a group of contributors who discuss political, economic, legal, public policy and biomedical issues in an imaginative, hard-hitting fashion. The "business as usual" approach of the large, multinational tobacco companies is analyzed. In particular, the effect of tobacco company diversification and economic clout on media coverage is assessed, and one is left with the sad conclusion that the media's editorial independence has been compromised by these developments. Perhaps a more ominous threat to world health is the pernicious movement of the multinational companies into the relatively underdeveloped markets of the third world. The devastating consequences of increasing tobacco consumption in these areas are described.

This volume contains a wealth of practical information on such issues as physician involvement with smoking cessation and public advocacy programs. Those concerned with promoting clean air acts in local communities will read with interest about the experience in Minnesota, Florida and Illinois. Activities of medical associations and physician groups around the world are detailed as examples of how physicians can and should become involved in dealing with the tobacco problem. The efforts of DOC (Doctors Ought to Care) are cited as creative approaches to countering tobacco advertising campaigns. Dr Blum organized DOC while he was a resident in family practice at the University of Miami School of Medicine in the 1970s.

In summary, because of its unique perspective on the major public health problem of our time, this volume is highly recommended for both physicians and nonphysicians. Dr Blum has succeeded in conveying an air of urgency concerning this problem and has detailed how physicians and other interested parties can help combat the tobacco industry's greedy pursuit of profits.

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COLOR ATLAS OF GERIATRIC MEDICINE—Asif Kamal, MBBS, MRCP, Consultant Physician in Geriatric Medicine, St George's Hospital, Lincoln, and J. C. Brocklehurst, MD, MSc, FRCP, Professor of Geriatric Medicine, University of Manchester, England. Medical Economics Books, Oradell, NJ 07649, 1984. 169 pages, $59.95.

The *Color Atlas of Geriatric Medicine* is a modest-sized volume that aims to illustrate special features of diagnosis in the elderly. The book opens with three short general chapters which include an introduction to the specialty of geriatrics, special features of illness in old age and assessment of the elderly patient. These chapters, while well written, are brief and superficial in their coverage. The first describes the field of geriatrics as it is practiced in Great Britain, and the structure of services will not be directly applicable to programs in the United States, though they provide a useful model.

The remainder of the book is composed of illustrated sections organized by anatomical areas. Each section includes color photographs demonstrating physical findings, and a variety of additional illustrations, including photographs of hematological slides, x-ray films, nuclear medicine scans, pathological specimens, diagrams and drawings. Each item has a brief descriptive caption. The text in these sections is limited to outline form listings of differential diagnoses, clinical features or pathophysiological mechanisms of the entities depicted. Most of the text is presented as tables.

The atlas contains an impressive array of photos of physical findings which would be quite useful to teaching clinicians. There is considerable overlap with general internal medicine, which is understandable given the nature of the field. However, there is pronounced variability in the type of illustrations chosen for different sections. For example, in the chapter on the head and neck, there are four photos of hearing aid devices but none of visual aids or dentures. The chapter on the lower extremity likewise does not depict assistive devices for ambulation. This inconsistency signals a lack of clear-cut overall purpose for the book.

There is a final chapter on hypothermia in the elderly which has an expanded text compared with the others. While hypothermia is a common problem in Great Britain, there are no other chapters on individual clinical syndromes and its presence again disrupts the organization of the book.

Due to its brevity, the Atlas fails in its stated purpose as a "comprehensive introduction to geriatric medicine." A more consistent approach from section to section, with greater restriction to physical diagnosis and topics quintessentially geriatric, would make the volume more cohesive. It would be a useful adjunct to more in-depth texts in the teachings of geriatric medicine to students and clinicians.

LISA HEIKOFF, MD
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TECHNOLOGY OF NUCLEAR MAGNETIC RESONANCE—Edited by Peter D. Esser, PhD, Department of Nuclear Medicine, College of Physicians and Surgeons, New York, and R. Eugene Johnston, PhD, University of North Carolina, Chapel Hill. The Society of Nuclear Medicine, Inc, 475 Park Ave South, New York, NY 10016, 1984. 257 pages, $29.00 (paperback).

Nuclear magnetic resonance (NMR) is, by far, the most complex technology yet to be applied in clinical medicine. This small, multiauthor volume attempts to shed light on the topic so that physicians not conversant with the subject can at least get a foot in the door of this fascinating field. It may be impossible for a NMR expert to explain the field to a novice. In all of its ramifications NMR is, and will probably remain, beyond the grasp of any one person.

This volume reflects what is probably too great a gap between author and reader. This should not be taken as excessively critical of this particular book because no one else has succeeded in making NMR comprehensible either.

There is a great deal of useful material presented here and available to those prepared to plow through the book. It presents a variety of topics in the area the title defines, and is divided into five sections: (1) overview, (2) pulse sequences and parameter extraction, (3) flow and motion, (4) new techniques and (5) installation considerations.

Only the first section requires advanced mathematical ability and much of this section is clearly written. The remainder of the volume contains practical information that will be of interest to anyone entering this dazzling field.

There are obvious practical limitations in this volume. It has been printed from "photo ready" typescript. This speeds publication but is less easily read. An index would have greatly strengthened the volume and its absence forces one to forage through the book. There are many pithy and useful facts buried in it.

This volume succeeds as well as any yet published in clarifying the NMR phenomenon as it applies to medicine. It is up-to-date—an important consideration in this rapidly changing field.

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MUTILATING INJURIES OF THE HAND, Second Edition—Edited by D. A. Campbell Reid, MB, BS, FFRCS, and R. Tubiana, in collaboration with 37 authors. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 212 pages, $55.

This monograph is one of a series sponsored by the Groupe D'Etude de la Main (GEM), and many of the chapters are based on papers originally written in French. In addition to the 26 French authors, there are 6 from Australia and others from England, India, Israel, Switzerland and Brazil. All are very experienced in the management of hand injuries.

The contents are divided into two parts: Primary treatment and secondary management of mutilated hands. Part I has seven chapters involving primary treatment, skin cover, unstable finger injuries, amputations and replantation procedures. Particular emphasis is placed on the importance of providing skin with normal sensibility on tactile surfaces. Part II has 26 chapters discussing digital transfers after amputation, phalangisation of metacarpals, distraction-lengthening techniques, microsurgical transfers, thumb reconstruction, the Krunkenberg operation, treatment of painful neuromata and amputation stumps, sensory flaps for the degloved hand, functional appliances, cosmetic prostheses, the results and postoperative management, reeducation and psychological problems in mutilating injuries.

The papers provide an excellent balance between proved techniques and developing expertise, such as microsurgery. The book will appeal to hand surgeons, orthopedic surgeons, plastic surgeons, physical therapists, occupational therapists, hand therapists, emergency room personnel and all other professionals called upon to treat these challenging cases. This revised second edition has been expanded to provide greater technical detail in this special surgical field.

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HOW TO SURVIVE MEDICAL SCHOOL—Toni Martin, MD. Penguin Books, 40 W 23rd St, New York, NY 10010, 1984. 180 pages, $5.95 U.S.A., $6.95 CAN (paperback).

How to Survive Medical School is an accurate and sensitive account of the emotional, physical and educational ups and downs of medical training. The author, Dr Toni Martin, recently completed her training in internal medicine at the University of California, San Francisco. All medical students and residents should identify with Dr Martin's experiences and reactions.

Written in a conversational tone, this book is short and easily read in one or two sittings. It deals with all aspects of medical education. There is a chapter devoted to each year, beginning with the application period and ending with the residency years. Additionally, there are two excellent chapters titled "The Real World" and "The Real World Revisited," which discuss the impact of medical training on the social and home life of the student.

Dr Martin has written an excellent book. She has recalled her training with perception and humor, but without a pair of rose-colored glasses. Those expecting a reminiscence about the "good old days" will be disappointed. The section on medical school emphasizes the different challenges and frustrations that accompany each year. She describes not only the intimidating curriculum, but also the difficult transition from classroom learning to wards learning. She recalls the uncertainty of the third-year student who must figure out her role in relation to the housestaff and the patients. The author discusses the difficulty of reconciling the uneasiness felt by the student when practicing on people with the need for a "hands on" education. Her section on residency is equally insightful. She tells of the fatigue and depression of an intern and the fear of a resident suddenly faced with the responsibility of a ward team.

Dr Martin has certainly given a fair amount of time to relating the positive aspects of training. Anecdotes appear throughout the book which show her new found (and hard earned) knowledge, competence and confidence. All of us can relate to the sense of accomplishment felt by the third-year student starting her first intravenous line, the intern managing her first case of pulmonary edema and the resident successfully running her first Code Blue.

Throughout the book, the author emphasizes the great impact that training has on interpersonal relationships both in and out of the hospital. She briefly touches on the prejudices that still exist for women and nonwhite physicians.

I recommend this realistic account of medical education for physicians at all levels. For premedical students, it may be disillusioning but should help them bring a set of reasonable expectations to medical school. This book may remind older physicians about the stresses under which their students are working. Most important, for physicians in training this book is comforting. It is reassuring to realize that the myriad of doubts and frustrations that accompany training today have been experienced by people who are currently enjoying their medical careers.

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* * *

RICHARD LOWER'S *VINDICATIO*—A DEFENCE OF THE EXPERIMENTAL METHOD—A facsimile introduced and edited by Kenneth Dewhurst, MD, FRHistS. Sandford Publications, Manor House, Sandford-on-Thames, Oxford, United Kingdom OX4 4YN, 1983. 314 pages, price: 12 English Pounds, limited to 250 numbered and signed copies.

It has been my pleasure on several previous occasions to review books by Kenneth Dewhurst, MD, of Oxford University. Like the book here reviewed, Professor Dewhurst's writings generally are concerned with the history of British medical and biological research of the 16th and 17th centuries and deal with the evolution of medical ideas and practices, rather than with the personal lives of individual physicians.

In this book, which follows the author's *Thomas Willis's Oxford Lectures* (Oxford, 1980) and *Willis's Oxford Casebook* (Oxford, 1981), Dewhurst reveals such familiarity with the concerns and interactions of the British physicians of the 17th century that it almost appears as if he had lived among them at that time. As the title and introduction indicate, there was an unending and unsparing flow of arguments, doubts and denials among medical colleagues about each other's theories and discoveries.

The subject matter of this book is again a work by Thomas Willis, *Treatise on Fevers,* which had been unmercifully criticized by a number of contemporary physicians but by none as fiercely as by the Irishman Edmund O'Meara. The fevers, discussed but not identified by Willis, are believed to have been the various epidemic fevers of the middle of the 17th century, such as purulent meningitis of which there was an epidemic in 1658 and encephalitis lethargica, an epidemic fever of 1661. There also were the various forms of intermittent fevers. Willis was able to write so authoritatively about these diseases because—as a very busy practitioner—he had much experience with a variety of patients suffering from these diseases.

It was logical that Richard Lower, who had been Willis's student and assistant, came to the defense of his teacher and wrote a *Vindicatio*, or justification, of Willis's work on fevers together with *A Defense of the Experimental Method*. It was this experimental method, largely derived from animal experimentation, that was rejected by O'Meara. Even though the latter's description of the nature and pathology of the blood flow and vascular infractions was correct and remarkably insightful, Lower, on one occasion, permitted himself to describe O'Meara as a "market quack."

O'Meara, the vociferous doubter of Willis's findings on fevers and fermentation, derived his power of conviction from his disbelief in Harvey's theory of the circulation of the blood. Another of his strong and unassailable prejudices was his distaste of all animal experimentation, because vivisection was seen by him purely as "terrible tortures." Any experimental evidence that contradicted his own ideas was disregarded by O'Meara.

All these developments and hostilities are beautifully detailed in Professor Dewhurst's introduction to this book. And to add fuel to the fire of dissention, a 194-page facsimile edition of the entire original Latin text of Richard Lower's justification of Thomas Willis's *Treatise on Fevers*, directed against Edmund O'Meara, is inserted in the center of the book.

This facsimile edition of Lower's defense of Willis's *Treatise on Fevers* makes Dewhurst's work doubly valuable, for not only can the reader compare Willis's own words which Lower so valiantly defends, but it also makes available complete copies of Lower's *Vindicatio* which cannot be obtained in any other fashion as the *Vindicatio* is one of the very rare books of medical history. It probably is as a means of preserving this rarity that the book here reviewed was published in a limited edition of 250 numbered and signed copies. Hence, even on purchasing a new volume of this interesting and learned volume, the modern physician will obtain a collector's item that will soon be irreplaceable.

ILZA VEITH, PhD, DmedSci
Professor Emeritus
Departments of Psychiatry and History of Health Sciences
University of California, San Francisco

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NEW MEXICO MEDICAL SOCIETY

SCIENTIFIC SESSION: HUMAN SEXUALITY UPDATE—1985

28th INTERIM SESSION

November 14-16, 1985

HOLIDAY INN DE LAS CRUCES
Las Cruces, NM

REGISTRATION

$45, members; after Nov 5—$50
$75, nonmembers; no fee for emeritus, nurses, students
$15, physicians in government service, residents

RESERVATIONS

HOLIDAY INN DE LAS CRUCES
201 East University
Las Cruces, NM 88001
(505) 526-4411

November 14, 1985

2:00 PM
COUNCIL MEETING

November 15,1985

8:30 AM
HOUSE OF DELEGATES—
First Meeting

9:15 AM
REFERENCE COMMITTEES

2:00 PM
SCIENTIFIC SESSION—
Human Sexuality Update—1985

"The Signs and Symptoms of Sexual Dysfunction"
J. ROBERT MEYNERS, PhD, MASTERS & JOHNSON INSTITUTE

"Age and Sexuality: The Mature/ Postmenopausal Woman"
WALTER G. LEONARD, MD, Boston, Massachusetts

"The Effects of Drugs on Libido"
ALLEN B. ADOLPHE, MD, Albuquerque

"Impotence: Cause and Effect"
ROBERT T. ROSEN, MD

7:00 PM
BANQUET

Speaker: J. R. MEYNERS, PhD
"Effective Treatment of Sexual Dysfunction—The Masters & Johnson Program"

November 16, 1985

9:00 AM
"Psycho-sexual and Psychological Implications of Body Image, Perceived and Real"
BURTON B. WEBER, MD

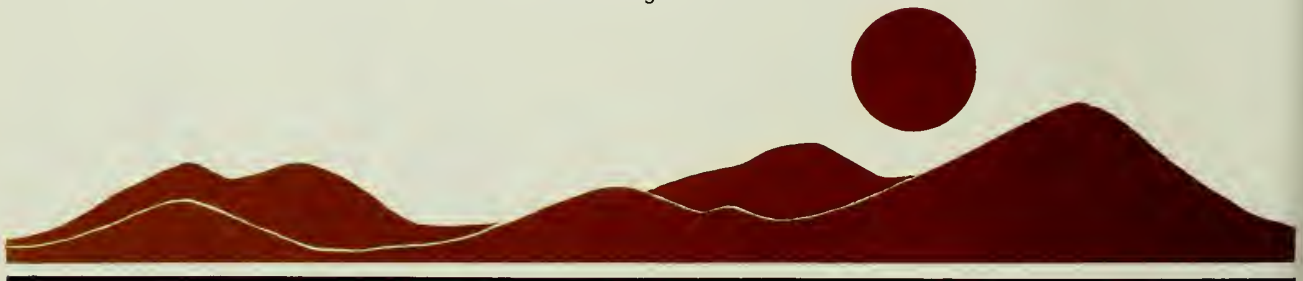
9:40 AM
"Sexual Fulfillment Despite Chronic Disease and Pain"
WALTER G. LEONARD, MD

10:30 AM
SMALL GROUP DISCUSSIONS

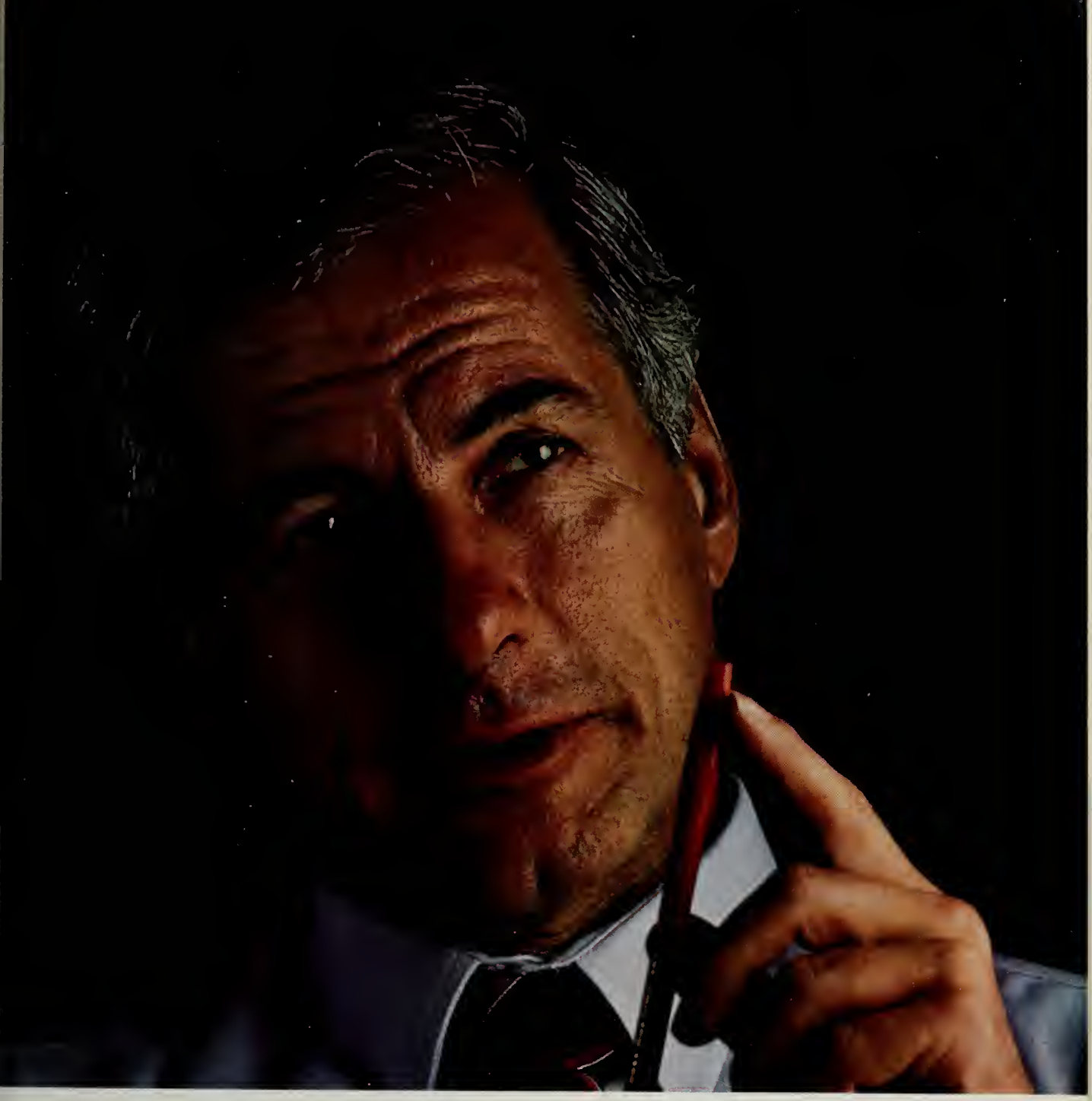
11:30 AM
SUMMATION

12:00 NOON
NEMPAC LUNCHEON/SEMINAR—
Political Awareness and Involvement for the Medical Community

2:00 PM
HOUSE OF DELEGATES—
Second Meeting



NEW MEXICO MEDICAL SOCIETY ■ 303 SAN MATEO BLVD., N.E., SUITE 204 ■ ALBUQUERQUE, NEW MEXICO 87108 ■ PHONE (505) 266-7868



"When the Ayerst rep told me it costs about 45¢ a day, I said you can stop right there."

Most doctors are pleasantly surprised to learn that the average cost of daily therapy with the world's most widely used beta blocker is so little, not much more than the cost of a daily newspaper.

When it's INDERAL (propranolol hydrochloride) tablets you want for your hypertension patients, remember to specify Dispense As Written (DAW) or Do Not Substitute on your prescriptions. That way, you can always be assured they'll get INDERAL®. Please see next page for brief summary of prescribing information.

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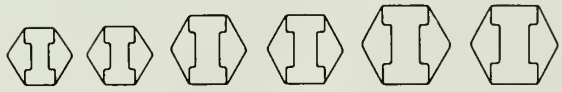

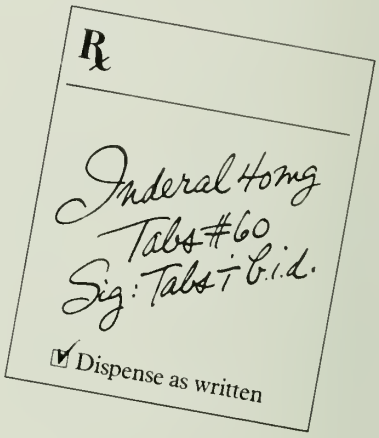

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia. LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

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New York, N.Y. 10017

(Continued from Page 460)

Surgery at Santa Barbara. Saturday-Sunday. Fee: $325. Contact: Joseph R. Dibartolomeo Ear Foundation, 2420 Castillo St., Santa Barbara, CA 93105. (805) 682-3711.

OF INTEREST TO ALL PHYSICIANS

October 16—**Alcohol and Drug Symposium.** Southern California Permanente at Pasadena Hilton Hotel, Pasadena. Wednesday. Contact: Judy Harrison, Dept. of Clinical Services, Southern California Kaiser-Permanente, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 17-20—**Clinical Biofeedback Certificate Program.** UCLA at Los Angeles. Thursday-Sunday. 24 hrs. $95.

October 17-20—**10th Annual Western Regional Meeting of the Society of Nuclear Medicine** at Palm Springs. Thursday-Sunday. Contact: Justine Parker, PO Box 40279, San Francisco, CA 94140. (415) 647-0722.

October 17-20—**Quality Care in the Workers Compensation System.** USC at Los Angeles. Thursday-Sunday. 21 hrs.

October 18-20—**Common Office Problems for the Primary Care Physician: 2nd Annual Symposium.** Monterey County Medical Society at Monterey. Friday-Sunday. 12 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

October 19—**Obesity, Brief Therapeutic Strategies for Preparing the Obese Person to Make Lasting Dietary Changes.** Mental Research Institute, 555 Middlefield Rd. at Palo Alto. Saturday. 3.5 hrs. Fee: $40. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 19-20—**Passionate Attachments: The Essential but Fragile Nature of Love.** Continuing Education Seminars at Century Plaza Hotel, Los Angeles. Saturday-Sunday. 12 hrs. $175. Contact: Continuing Education Seminars, 1023 Westholme Ave., Los Angeles, CA 90024. (213) 475-8300.

October 21-24—**Family Crises: Intervention Strategies.** Mental Research Institute at Palo Alto. Monday-Thursday. 12 hrs. Fee: $170. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

October 23-27—**Sexual Abuse: An Interdisciplinary Exploration.** Southern California Neuropsychiatric Institute at Ritz-Carlton, Laguna Niguel. Wednesday-Sunday. Fee: $350. Contact: Stacey W. Grace, La Jolla Blvd., La Jolla 92037. (619) 454-2102.

October 25-27—**Child Abuse.** Institute for the Advancement of Human Behavior at Anaheim. Friday-Sunday. 15 hrs. $145-$225. Contact: IAHB, 4370 Alpine Road, #205, Portola Valley, CA 94025. (415) 851-8411.

October 25-29—**The Spine: Advanced Concepts and Techniques.** The Spine Study Group at Vacation Village Hotel, San Diego. Friday-Tuesday. Contact: Spine Study Group, PO Box 13185, San Diego, CA 92103. (619) 692-9115.

October 26—**Symposium on Infectious Disease: Diagnosis and Treatment in the Office Practice.** Center for Healthcare Communications at Hilton Hotel, Sacramento. Saturday. 6 hrs. Contact: Pamela Harvey, Center for Healthcare Communications, 420 Lexington Ave., #320, New York, NY 10017. (212) 210-8940.

November 1-2—**Treating the Emotional Aspects of Cardiovascular Disease.** Monterey County Medical Society at Napa Valley. Friday-Saturday. 6 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

November 6-8—**Primary Care: Selected Current Topics.** Merritt-Peralta Health Education Center at Oakland. Wednesday-Friday. 18 hrs. Fee: $245. Contact: Merritt-Peralta, 400 Hawthorne Ave., Oakland. (415) 420-6161.

November 7-10—**Adult Children of Alcoholics.** St. Luke's Hospital at Los Angeles. Thursday-Sunday.

November 7-10—**Academy of Psychosomatic Medicine Annual Meeting.** Academy of Psychosomatic Medicine at San Francisco. Thursday-Sunday. Contact: Evelyne Hallberg, APM, 70 W. Hubbard St., Chicago, Ill 60610. (312) 644-2623.

November 8—**New Concepts in Medicine—21st Annual Staff Seminar.** California Medical Center at Los Angeles. Friday. 6 hrs. Fee: $35. Contact: Kenneth L. Senter, MD, Director of Medical Education, 1414 S. Hope St., Los Angeles 90015. (213) 748-4211.

November 8-9—**Update of the Treatment of Asthma.** Monterey County Medical Society at Monterey. Friday-Saturday. 6 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

November 14-15—**California Tuberculosis Controllers Fall Meeting.** California Tuberculosis Controllers Association at San Bernardino. Thursday-Friday.

November 14-16—**Clinical Preventive Medicine: 1985.** UCD at Sacramento. Thursday-Saturday. Contact: Office on Continuing Medical Education, 2701 Stockton Blvd., Sacramento 95817. (916) 453-5390.

November 15-17—**Injured Runner Seminar.** UCSD. Friday-Sunday. 19 hrs. Contact: Isabelle S. Green, Camp International Inc., Box 89, Jackson, MI 49204-0089. (517) 787-1600, ext. 291.

November 16—**Systematic Aspects of Chronic Physical Pain.** Mental Research Institute at Palo Alto. Saturday. 5 hrs. Fee: $70. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

December 6-7—**Clinical Nutrition Update for the Practicing Physician.** UCD at Sacramento. Friday-Saturday. Contact: Office of CME, School of Medicine, UCD, 2701 Stockton Blvd., Sacramento, CA 95817. (916) 453-5390.

December 14-21—**Current Concepts in Pain Management.** International Conferences at Hawaii. One Week. 20 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

IDAHO

February 1-8—**Sports Medicine.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 8-15—**Orthopaedics/Radiology.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 15-22—**Endocrinology/Diabetes.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

MONTANA

See Montana listings under WASHINGTON.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 17-19—**Primary Care Update '85: A Clinical Symposium for Physician Assistants, Nurse Practitioners and Allied Health Professionals.** Albuquerque. Thursday-Saturday. AMFAC Hotel. Contact: UNM.

November 1—**The Treatment of Coronary Artery Disease.** Albuquerque. Friday. 8 hrs. AMA Cat. I. Continental Inn. Contact: American Heart Association-New Mexico Affiliate, 629 Truman NE, Albuquerque 87108. (505) 268-3711.

November 1-2—**New Mexico Pediatric Society Annual Meeting—Infectious Diseases in Children.** Ruidoso. Friday-Saturday. Inn of the Mountain Gods. 8 hrs. AMA Cat. I. Contact: NM Pediatric Society, Marilyn Stark, Executive Secretary, 7605 Mountain Rd. NE, Albuquerque 87110. (505) 293-1333.

November 15-16—**New Mexico Medical Society Interim Meeting—Human Sexuality Update—1985.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. 6 hrs. AMA Cat. I. Contact: NM Medical Society, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

November 22—**Current Concepts on Causes of Cancer.** Los Alamos. Friday. Los Alamos National Labs, Meson Facility. 6 hrs. AMA and NM Cat. I. Contact: Jerry Williams, MD, PO Box 1663, MS-D421, Los Alamos 87545.

November 22-23—**Infectious Disease Update.** Albuquerque. Friday-Saturday. Sheraton Old Town. 10 hrs. AMA Cat. I. Contact: Lovelace Medical Center, Office of CME, 5400 Gibson SE, Albuquerque 87108. (505) 262-7353.

December 5-7—**New Mexico Chapter, American College of Physicians, and New Mexico Society of Internal Medicine**—Annual Meetings. Thursday-Saturday. Marriott Hotel, Albuquerque. 12 hrs. AMA Cat. I. Contact: UNM.

December 13-14—**Trauma Update '85.** Albuquerque. Friday-Saturday. Convention Center. AMA Cat. I. Contact: UNM.

February 20-22—**19th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. Hilton Inn. AMA Cat. I. Contact: UNM.

CONTACT INFORMATION

UNM—Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

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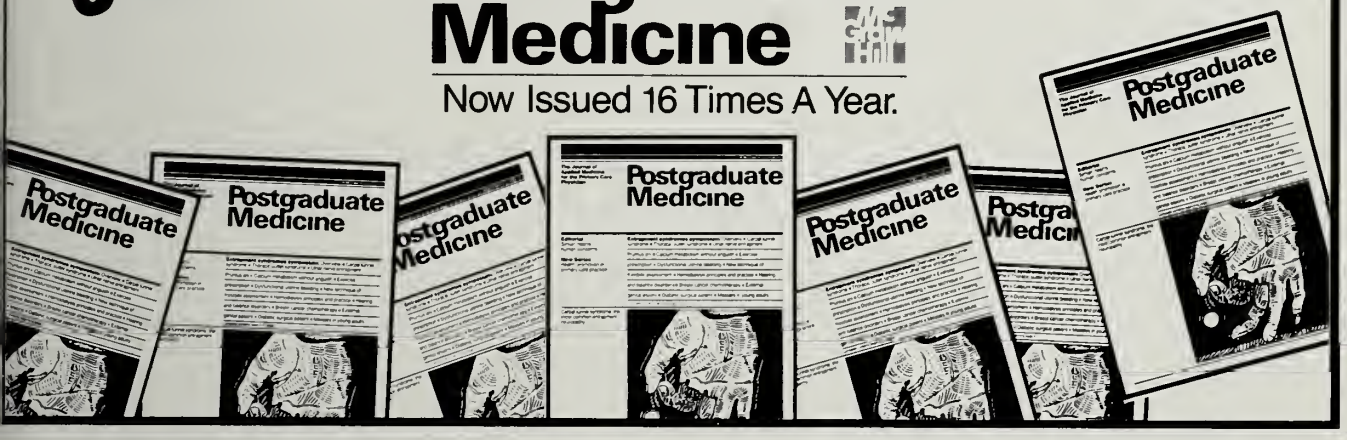

CONTINUING MEDICAL EDUCATION

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences Univrsity, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

EMERGENCY MEDICINE

November 14-15—**Symposium on Critical Care Medicine.** Red Lion/Jantzen Beach. Thursday-Friday. Contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 17-19—**9th Annual Pacific NW Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion/Jantzen Beach. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

November 8-9—**Advanced Trauma Life Support** (Sponsor: University of Utah/Utah Department of Health). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Kim Tanner, (801) 533-6608.

January 20-23—**International Biomedical Engineering Symposium** (Sponsor: University of Utah). Monday-Thursday. Salt Lake City Salt Palace. 18 hrs. Contact: Joseph Andrade, PhD, (801) 581-7236.

April 10-12—**Neurology for the Practitioner** (Sponsor: University of Utah). Thursday-Saturday. Salt Lake City Sheraton. 18 hrs. Contact: J. Richard Baringer, MD, (801) 581-8664.

March 6-7—**Utah Ophthalmological Society Annual Park City Winter Meeting: Corneal Disease** (Sponsors: Utah Ophthalmological Society and University of Utah). Thursday-Friday. Holiday Inn/Yarrow, Park City. Contact: Pam Hanson, (801) 355-5290.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

(Continued on Page 559)

DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (lorazepam) for Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

Wyeth Laboratories
Philadelphia, PA 19101

Only Ativan® (lorazepam) IV

offers all these benefits in addition to rapid relief of anxiety:

relief of anxiety associated with depressive symptoms

clearance not significantly delayed by age, liver or kidney dysfunction

cumulative sedative effects seldom a problem

little likelihood of drug interaction
(all benzodiazepines produce additive effects when taken with alcohol or other CNS depressants)

no significant changes in vital signs in cardiovascular patients*

short duration of action, simple metabolism

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

See important information on preceding page.

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Wyeth Laboratories
Philadelphia, PA 19101

(Continued from Page 557)

October 15—**Physiology of Aging.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

October 17-18—**Washington State Hospital Association—Annual Meeting.** Seattle. Thursday-Friday. Red Lion Inn. Contact: Wendy Ray, WSHA, 190 Queen Anne Avenue North, Seattle 98109. (206) 281-7211.

October 18—**Annual Cancer Conference.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 18—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

October 22—**Death Investigations.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

October 24-25—**Alzheimer's.** Seattle. Thursday-Friday. Holiday Inn, Crowne Plaza. Contact: U/W.

October 25—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

October 25-26—**Neonatal and Pediatric Advanced Life Support.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 26—**Transdermal Therapy.** Seattle. Saturday. Westin Hotel. Contact: U/W.

November 1—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 1-2—**Preventive Cardiology and Medical Alumni Day.** Seattle. Friday-Saturday. U/W Health Sciences. Contact: U/W.

November 1—**Management of Common Problems in Epilepsy.** Bellevue. Friday. Red Lion Inn. Contact: Nancy Aziz, Continuing Medical Education, Overlake Hospital and Medical Center, 1035 116th Ave. NE, Bellevue 98004. (206) 454-4011, ext. 2630.

November 1—**Frontiers in Eye Care for Health Professionals.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 1-2 (VANCOUVER)—**Northwest Urological Society 1985 Annual Meeting.** Vancouver, BC. Friday-Saturday. Bayshore Inn. Contact: Patti Smith, Northwest Urological Society, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

November 7-8—**Washington Chapter, American College of Emergency Physicians—15th Annual Clinic Conference.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington Chapter, ACEP, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

November 7-8—**Drug Therapy.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

November 8—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 13 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Columbus Hospital. Contact: U/W.

November 14 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

November 15—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 15 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

November 15—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 15-16—**Seafood and Health Conference.** Seattle. Friday-Saturday. Seattle Sheraton. Contact: U/W.

November 19—**Common Knee Problems.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

November 21—**Pacific Northwest Endoscopy Society.** Seattle. Thursday. Four Seasons Olympic. Contact: U/W.

November 23-30 (HAWAII)—**Medical Malpractice: Preventive Approach.** Maui. One week. Royal Lahaina. Contact: U/W.

November 26—**Office Dermatology.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

November 29-30—**Syposium on Breast Disease.** Seattle. Friday-Saturday. Seattle Sheraton. Contact: U/W.

November 29—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 30-December 1—**Immediate Care of Sick and Injured.** Seattle. Saturday-Sunday. U/W Health Sciences. Contact: U/W.

December 5-6—**Aging and the Elderly.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

December 6—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 6—**Practical Pediatrics.** Scattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 7—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

December 7-8—**Washington State Society of Anesthesiologists Winter Meeting.** Seattle. Saturday-Sunday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

December 11—**Hypertension.** Seattle. Wednesday. Westin Hotel. Contact: U/W.

December 13—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 17—**Rheumatoid Arthritis—1985.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

December 20—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 27-January 3 (HAWAII)—**Advances in Internal Medicine.** Kauai. One week. Waiohai Hotel. Contact: U/W.

December 27-January 3 (HAWAII)—**Medical Malpractice: Preventive Approach.** Kauai. One week. Waiohai Hotel. Contact: U/W.

January 3—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 10—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 14—**Osteoporosis: DX and RX.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

January 17-18—**Advances in Internal Medicine.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

January 17—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 21—**Immunization Updates.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

January 22 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

January 23 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

January 23-24—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

January 24-25—**Eye Care for Primary MDs.** Seattle. Friday-Saturday. Westin. Contact: U/W.

January 24—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 24 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

January 30-31—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

January 31—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 1-8 (IDAHO)—**Sports Medicine.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 6-7—**Neurology Update.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

February 7—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 7-8—**Clinical Problems in Urology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 8-15 (IDAHO)—**Orthopaedics/Radiology.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 14—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 15-22 (IDAHO)—**Endocrinology/Diabetes.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 18—**Antiviral Strategies.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

February 19 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Columbus Hospital. Contact: U/W.

February 20 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

February 20-22 (HAWAII)—**Father Damien's Colony.** Molokai. Thursday-Saturday. Sheraton Molokai. Contact: U/W.

February 21—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 21 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

February 23-March 1 (HAWAII)—**Trauma/Surgery.** Kona. Sunday-Saturday. Royal Waikoloa. Contact: U/W.

February 25—**Child Rearing Practices.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

February 28—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 28-March 1—**Neurology—Past, Present, Future.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

(Continued on Page 562)

ALZHEIMER'S DEMENTIA

Cure of the disease is still out of reach. In as devastating a condition as this, even the most modest relief of symptoms—or for that matter keeping them from getting worse or merely slowing their intensification—is a great contribution to patient and family.

HYDERGINE® LC (ergoloid mesylates) is indicated for patients over age sixty who manifest signs and symptoms of idiopathic mental decline. It appears that individuals who respond to HYDERGINE LC therapy are those who would be considered to suffer from some ill-defined process related to aging or to suffer from some underlying condition such as Alzheimer's dementia.

Before prescribing HYDERGINE therapy, the possibility that the patient's signs and symptoms arise from a potentially reversible and treatable condition should be excluded. In addition, because the presenting clinical picture may evolve to suggest an alternative treatment, the decision to use HYDERGINE therapy should be continually reviewed.

HYDERGINE® LC
(ergoloid mesylates)
liquid capsules, 1 mg

THE ONLY PRODUCT INDICATED FOR ALZHEIMER'S DEMENTIA.

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HYD-1085-13

For Brief Summary, please see following page.

HYDERGINE® LC
(ergoloid mesylates) liquid capsules 1 mg

Indications: Symptomatic relief of signs and symptoms of idiopathic decline in mental capacity (i.e., cognitive and interpersonal skills, mood, self-care, apparent motivation) in patients over sixty. It appears that individuals who respond to HYDERGINE therapy are those who would be considered clinically to suffer from some ill-defined process related to aging or to have some underlying dementing condition, such as primary progressive dementia, Alzheimer's dementia, senile onset, or multi-infarct dementia. Before prescribing HYDERGINE® (ergoloid mesylates), the physician should exclude the possibility that signs and symptoms arise from a potentially reversible and treatable condition, particularly delirium and dementiform illness secondary to systemic disease, primary neurological disease, or primary disturbance of mood. Not indicated for acute or chronic psychosis regardless of etiology (see Contraindications).

Use of HYDERGINE therapy should be continually reviewed, since presenting clinical picture may evolve to allow specific diagnosis and specific alternative treatment, and to determine whether any initial benefit persists. Modest but statistically significant changes observed at the end of twelve weeks of therapy include: mental alertness, confusion, recent memory, orientation, emotional lability, self-care, depression, anxiety/fears, cooperation, sociability, appetite, dizziness, fatigue, bothersome(ness), and overall impression of clinical status.

Contraindications: Hypersensitivity to the drug; psychosis, acute or chronic, regardless of etiology.

Precautions: *Because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing HYDERGINE (ergoloid mesylates) preparations.*

Adverse Reactions: Serious side effects have not been found. Some transient nausea and gastric disturbances have been reported, and sublingual irritation with the sublingual tablets.

Dosage and Administration: 1 mg three times daily. Alleviation of symptoms is usually gradual and results may not be observed for 3-4 weeks.

How Supplied: HYDERGINE LC (liquid capsules); 1 mg, oblong, off-white, branded "HYDERGINE LC 1 mg" on one side, "Ⓢ" other side. Packages of 100 and 500. (Encapsulated by R. P. Scherer, N.A., Clearwater, Florida 33518).

HYDERGINE (ergoloid mesylates) tablets (for oral use); 1 mg, round, white, embossed "HYDERGINE 1" on one side, "Ⓢ" other side. Packages of 100 and 500.

Each liquid capsule or tablet contains ergoloid mesylates USP as follows: dihydroergocornine mesylate 0.333 mg, dihydroergocristine mesylate 0.333 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.333 mg, representing a total of 1 mg.

Also available: HYDERGINE sublingual tablets; 1 mg, oval, white, embossed "HYDERGINE" on one side, "78-77" other side. Packages of 100 and 1000. 0.5 mg, round, white, embossed "HYDERGINE 0.5" on one side, "Ⓢ" other side. Packages of 100 and 1000.

HYDERGINE liquid; 1 mg/ml. Bottles of 100 mg with an accompanying dropper graduated to deliver 1 mg. [HYD--ZZ24--6 15 84]

Before prescribing, see package circular for full product information. HYD-1085-13

DORSEY PHARMACEUTICALS
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CONTINUING MEDICAL EDUCATION

(Continued from Page 560)

March 7—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 14—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 15-22 (HAWAII)—**Death Investigation.** Maui. One week. Royal Lahaina. Contact: U/W.

March 15-22 (HAWAII)—**Advanced Cardiac Life Support.** Kauai. One week. Kauai Sheraton. Contact: U/W.

March 18—**Shoulder Injuries.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 19 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

March 20 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

March 21 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

March 21—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 21-22—**Medicine for Psychotherapists.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

March 22—**Radiology Northwest.** Seattle. Saturday. UW Health Sciences Building. Contact: U/W.

March 22-29 (HAWAII)—**Ortho/OBGYN/Pain/Obesity/Surgery.** Kauai. One week. Kauai Sheraton. Contact: U/W.

March 25—**What's New In Imaging.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 28—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 3-4—**Oncology.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

April 4—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 5—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 5-12 (HAWAII)—**Drug Therapy.** Kauai. One week. Sheraton Princeville. Contact: U/W.

April 7-18—**Rehab Medicine Review.** Seattle. Monday-Friday. Seattle Sheraton. Contact: U/W.

April 11—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 15—**Reflux and Surgery.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 16 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Columbus Hospital. Contact: U/W.

April 17 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

April 18—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 18 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

April 22—**Common Knee Strains/Sprains.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

April 25—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 1-5—**Psychomotor Skill.** Seattle. Thursday-Monday. Westin Hotel. Contact: U/W.

May 2—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 2-3—**Functional Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8-9—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

May 9—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 16—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 20—**Hyperlipidemias.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 21 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

May 22 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

May 23 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

May 23—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 27—**Hyperlipidemia.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

May 30—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W. ◆

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Staff Researcher-Will be responsible for all formulation and drug delivery activities associated with the research and development of new and/or improved delivery systems for topically applied drugs. Will conduct basic research in physical pharmacy in areas of emulsion, multiple emulsion, micro-emulsion, liposomes and gel systems using drug molecules. Requires a PhD in pharmaceutical sciences. Must have done academic research of drug transfer in dispersed systems. Academic background must include coursework in differential equation and vector analysis, statistics, surface and colloid chemistry, particularly emulsion and liposome technology. Must have a thorough knowledge of diffusion cell systems. Job site: Palo Alto, CA. Salary: $37,500/yr. Send resume to Job #1300, P.O. Box 9560, Sacramento, CA 95823-0560 no later than November 10, 1985. EOE.

THE WESTERN JOURNAL OF MEDICINE

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

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Journal Articles

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1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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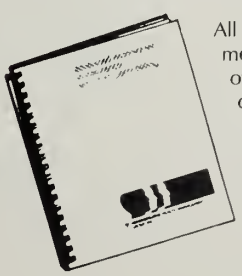

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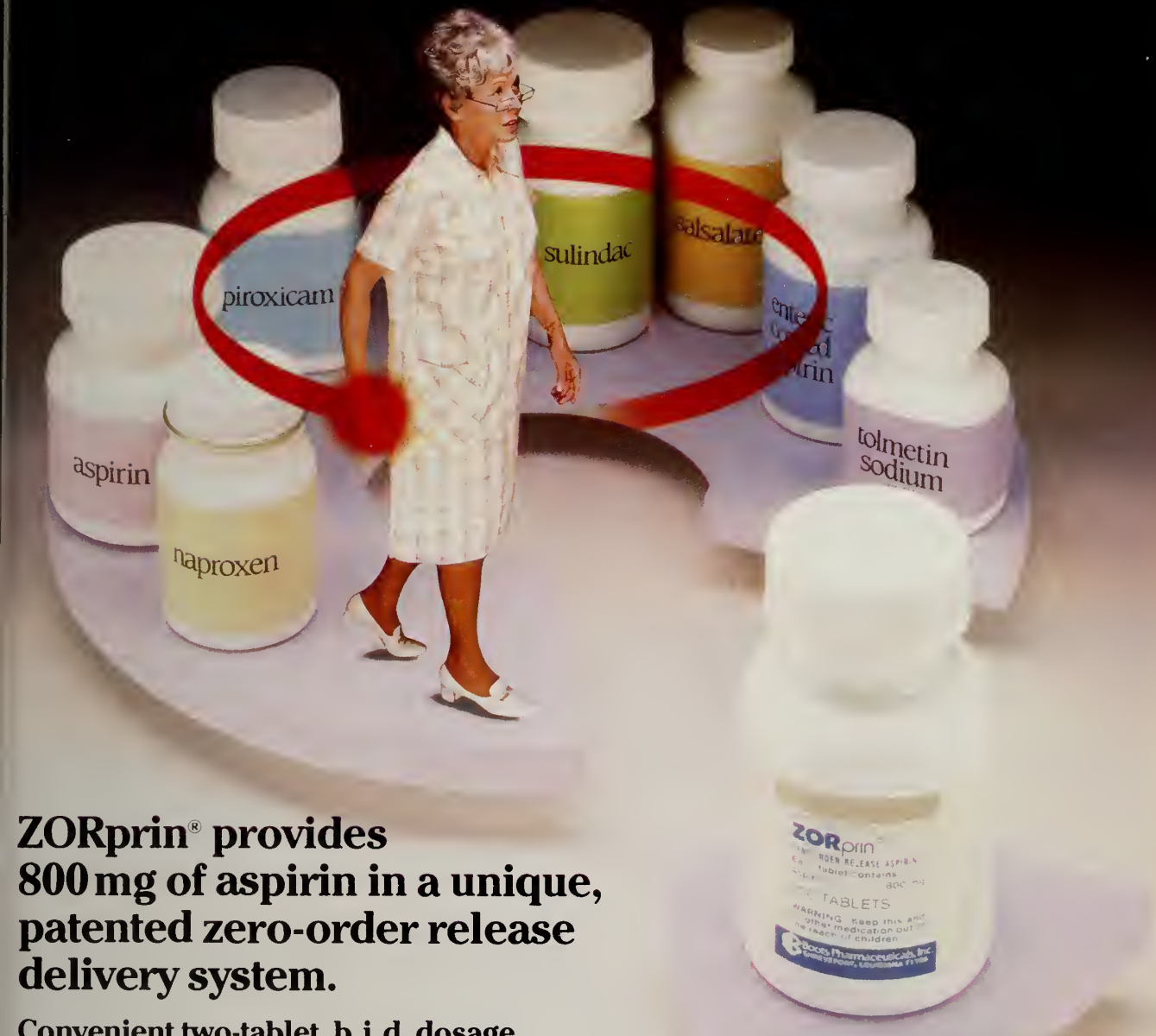

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Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledge in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

AMA HANDBOOK OF POISONOUS AND INJURIOUS PLANTS—Dr Kenneth F. Lampe and Mary Ann McCann, Division of Drugs and Technology, American Medical Association, 1985. 431 pages, with 437 illustrations in color, available from Chicago Review Press, 213 West Institute Place, Chicago, IL 60610, for $18.50, plus $2.50 UPS delivery and handling, and available at bookstores.

BIOCHEMISTRY AND THE CENTRAL NERVOUS SYSTEM—5th Edition—Henry McIlwain, PhD, DSc, Emeritus Professor, University of London, and Visiting Professor, Department of Biochemistry, St Thomas's Hospital Medical School, and Herman S. Bachelard, PhD, DSc, FBiol, Professor of Biochemistry, St Thomas's Hospital Medical School, University of London, and Honorary Consultant, St Thomas's Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 609 pages, $69.

THE CIGARETTE UNDERWORLD—Edited by Alan Blum, MD, Editor, *New York State Journal of Medicine*. Lyle Stuart Inc, 120 Enterprise Avenue, Secaucus, NJ 07094, 1985. 128 pages, $9.95.

CLINICAL PHARMACOLOGY OF DRUG DEPENDENCE—Pier Francesco Mannaioni, Professor of Toxicology, University of Florence, Florence, Italy. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Court, St Louis, MO 63043, 1985. 272 pages, $23.50 (paperback).

COMPUTED TOMOGRAPHY OF THE PELVIS—Volume 6 in Contemporary Issues in Computed Tomography—Edited by James W. Walsh, MD, Associate Professor of Radiology, Virginia Commonwealth University; Director, Diagnostic Oncologic Radiology, and Co-Director, Body Imaging Section, Department of Radiology, Medical College of Virginia Hospitals, Richmond. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 262 pages, $39.

CONSENSUS AND PENALTIES FOR IGNORANCE IN THE MEDICAL SCIENCES—IMPLICATIONS FOR INFORMATION TRANSFER—Edited by J. Michael Brittain, Department of Library and Information Studies, Loughborough University of Technology, United Kingdom. Taylor Graham, 500 Chesham House, 150 Regent St, London W1R 5FA, 1985. 188 pages, $22 (paperback).

CORRELATIVE NEUROANATOMY AND FUNCTIONAL NEUROLOGY—19th Edition—Joseph G. Chusid, MD, Professor of Neurology Emeritus, New York Medical College; Director of Department of Neurology Emeritus, St Vincent's Hospital and Medical Center, New York. Lange Medical Publications, Drawer L, Los Altos, CA 94023, 1985. 512 pages, $19.50 (softbound).

CURRENT EMERGENCY DIAGNOSIS AND TREATMENT—2nd Edition—Edited by John Mills, MD, Associate Professor of Medicine, Microbiology and Clinical Pharmacy, University of California, San Francisco, and Chief of Infectious Disease Unit, San Francisco General Hospital; Mary T. Ho, MD, Acting Assistant Professor of Medicine, Emergency Medicine Service, University Hospital, University of Washington, Seattle; Patricia R. Salber, MD, Clinical Instructor of Medicine, University of California, San Francisco, and Staff Physician, Emergency Department, Kaiser Permanente Medical Group, San Francisco; Donald D. Trunkey, MD, Professor of Surgery, University of California, San Francisco, and Chief of Surgery, San Francisco General Hospital, with associate authors. Lange Medical Publications, Drawer L, Los Altos, CA 94023, 1985. 864 pages, $28.

CURRENT EMERGENCY THERAPY '85—Edited by Richard F. Edlich, MD, PhD, Distinguished Professor, Plastic Surgery and Biomedical Engineering, and Director, University of Virginia Burn Center, University of Virginia School of Medicine, Charlottesville; Daniel A. Spyker, PhD, MD, Assistant Professor of Internal Medicine, and Co-Director, Blue Ridge Poison Center, University of Virginia School of Medicine, with Beth B. Haury, Editor, *Emergency Medicine*, University of Virginia School of Medicine. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1985. 1,098 pages, $85.

EARLY PARENTHOOD—HEAVEN OR HELL—Beverley Chalmers, PhD, School of Psychology, University of the Witwatersrand, Johannesburg; illustrated by Roger Titley. Juta & Co, Ltd, PO Box 123, Kenwyn 7790 South Africa, 1984. 244 pages (softbound), price not given.

ENDOCRINE TUMOURS—The Pathobiology of Regulatory Peptide-Producing Tumours—Julia M. Polak, DSc, MD, MRCPath, Reader in Histochemistry, Royal Postgraduate Medical School, and Consultant Histopathologist, Hammersmith Hospital, and Stephen R. Bloom, MA, MD, DSc, FRCP, Professor of Endocrinology, Royal Postgraduate Medical School, Hammersmith Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 280 pages, $59.

GENETICS AND NEUROLOGY—Sarah Bundey, MB, FRCP, Clinical Assistant and Lecturer in Clinical Genetics, Infant Development Unit, Queen Elizabeth Medical Centre, Birmingham, UK, and E. M. Brett, DM, FRCP, Consultant Neurologist, The Hospital for Sick Children, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 331 pages, $50.

HISTOCHEMISTRY—THEORETICAL AND APPLIED—Vol 2—Analytical Technology—4th Edition—A. G. Everson Pearse, MA(Cambridge), MD, FRCP, FRCPath, DCP(London), Emeritus Professor of Histochemistry, University of London (Royal Postgraduate Medical School), and Consultant Pathologist, Hammersmith Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 1,033 pages, $125.

INFERTILITY: A PRACTICAL GUIDE FOR THE PHYSICIAN—2nd Edition—Edited by Mary G. Hammond, MD, Assistant Professor and Director, Division of Reproductive Endocrinology and Fertility, and Luther M. Talbert, MD, Professor, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1985. 196 pages, $17.50* plus $2 for handling. *Prices are subject to change without notice.

MANAGEMENT OF HIGH-RISK PREGNANCY—2nd Edition—Edited by John T. Queenan, MD, Professor and Chairman, Department of Obstetrics and Gynecology, Georgetown University School of Medicine, and Obstetrician-Gynecologist-in-Chief, Georgetown University Hospital, Washington, DC; Editor-in-Chief, *Contemporary Ob/Gyn*. Medical Economics Books, 680 Kinderkamack Rd, Oradell, NJ 07649, 1985. 701 pages, $49.95.

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(Continued on Page 572)

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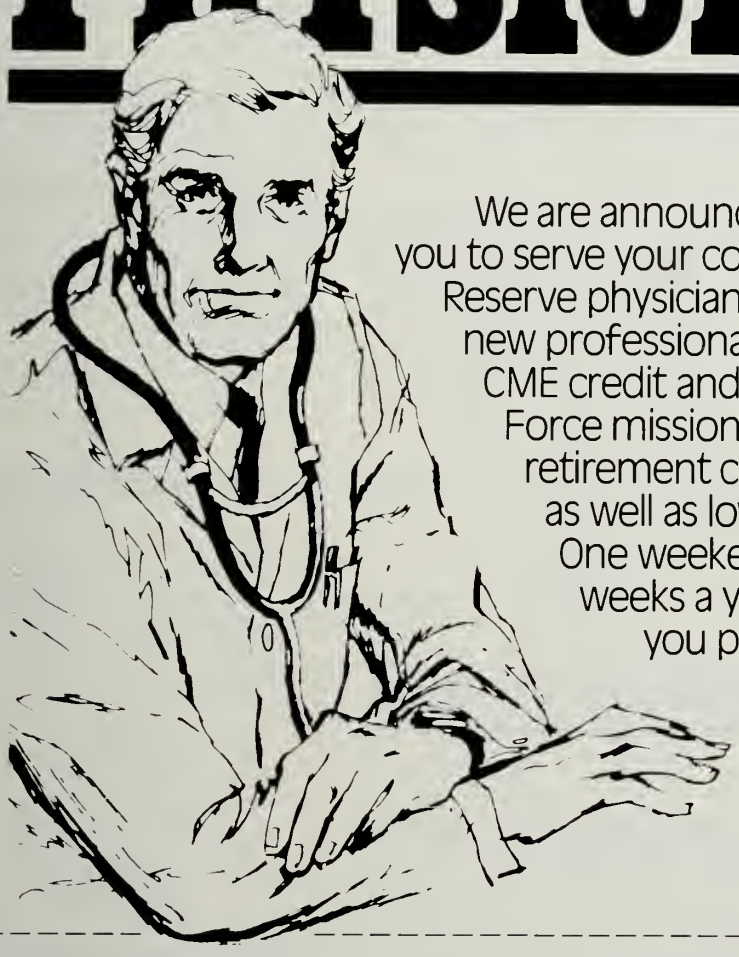

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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: June 5-7, 1986, Loews Ventana Canyon Resort, Tucson.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1986: date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1986: date and place to be announced.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 2-4, 1986, Winnemucca.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Interim Meeting: November 15-16, 1985, Holiday Inn de Las Cruces, Las Cruces. Centennial Meeting: April 30-May 2, 1986, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 25-27, 1986, Valley River Inn, Eugene.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1986: date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: 1986: date and place to be announced.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1986, Jackson Lake Lodge, Moran.

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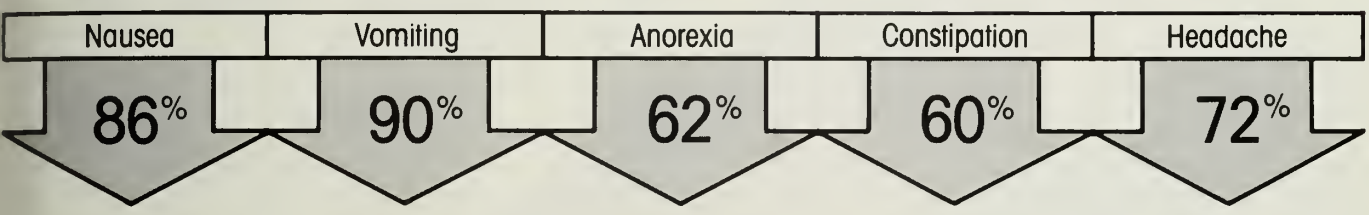

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Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets*, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets*, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Available in bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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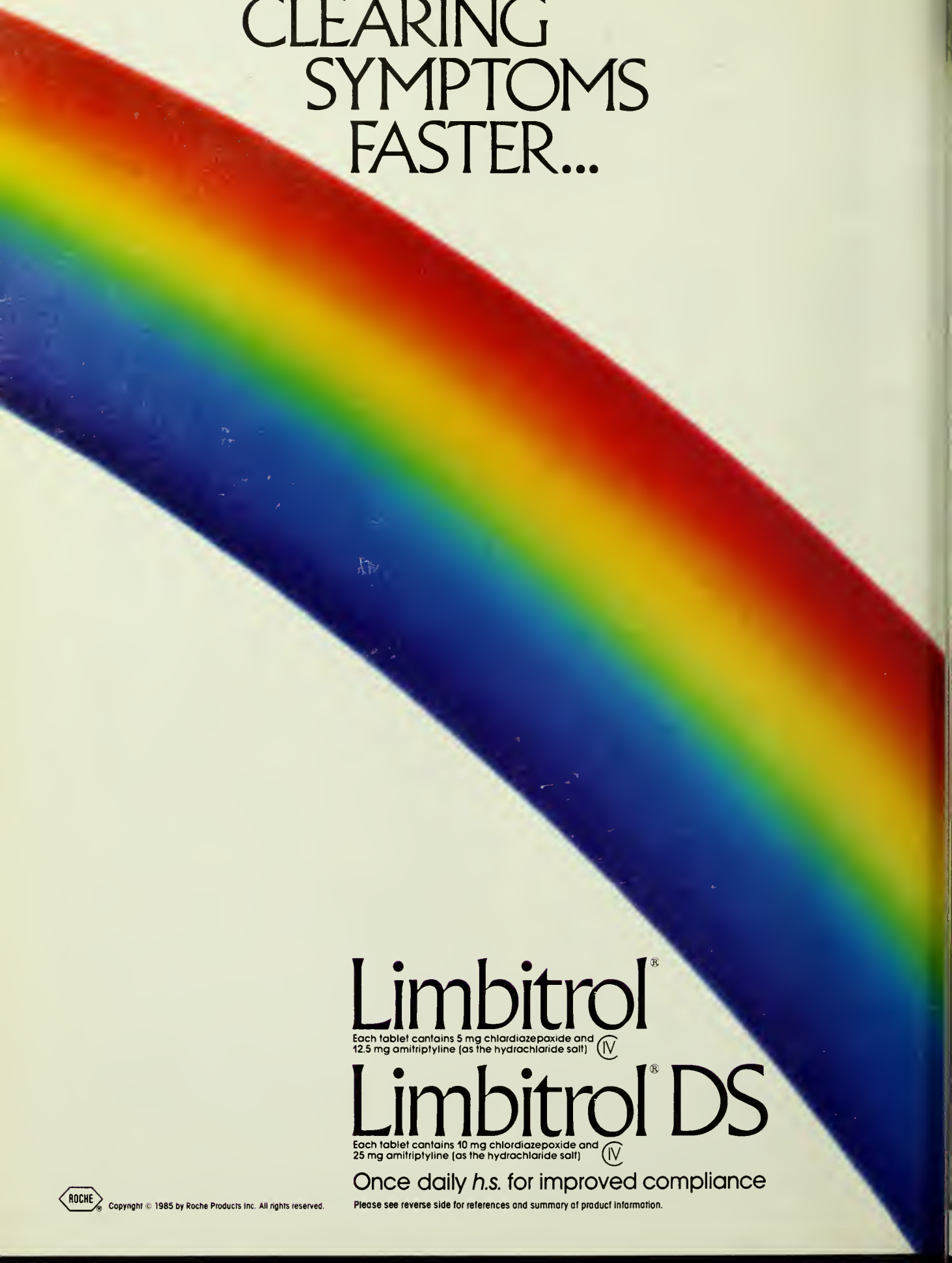

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Each tablet contains 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) (IV)

Limbitrol® DS

Each tablet contains 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) (IV)

Once daily *h.s.* for improved compliance

Please see reverse side for references and summary of product information.

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before Otoscopic view of tympanic membrane in a patient who did not respond to ampicillin

after Same patient after ten days of Bactrim (trimethoprim and sulfamethoxazole/Roche) therapy

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Active against 91% of *S. pneumoniae in vitro*

In sputum cultures of *Streptococcus pneumoniae,* the most frequent pathogen in acute otitis media, 91% of isolates show susceptibility *in vitro* to Bactrim.[4]

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In comparative clinical trials in children with acute otitis media, Bactrim *b.i.d.* was unsurpassed by ampicillin, amoxicillin or cefaclor.[6]
And the average cost of Bactrim is lower than that of cefaclor and comparable to that of ampicillin and amoxicillin.[7]
Bactrim is indicated in acute otitis media due to susceptible organisms when it offers an advantage over other antimicrobials. Bactrim is contraindicated in pregnancy, lactation, infants under two months of age and documented megaloblastic anemia due to folate deficiency. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age.

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References: 1. Klimek JJ *et al: J Pediatr 96:*1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Dis 4:*514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner 217:*804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs 24:*459-518, Dec 1982. 7. *Med Lett Drugs Ther 23:*93-95, Oct 30, 1981.

Please see summary of product information on the following page.

References: 1. Klimek JJ *et al*: *J Pediatr* 96:1087-1089, Jun 1980. 2. Schwartz RH *et al*: *Rev Infect Dis* 4:514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983, BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. 7. *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: ***Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.*** **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phospbate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform freqnent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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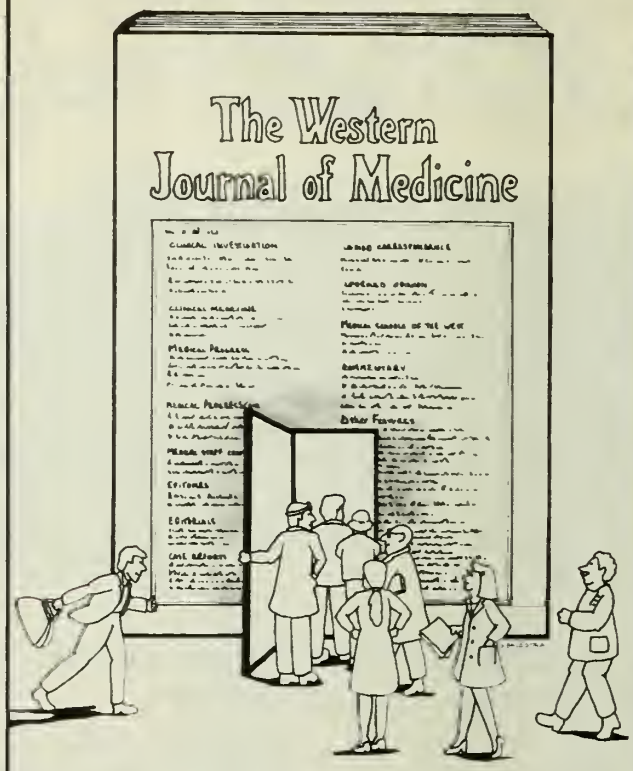

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SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8 hour duration of action of oral isosorbide dinitrate following the first dose (after a 2 week placebo washout) and only a 2 hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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Sustained Action "Swallow" Tablets

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656 **Clinical Basis for Treating Presumptive Chlamydial Infection**
JULIUS SCHACHTER, PhD

657 **Polysaccharide Vaccine for Preventing *Hemophilus influenzae* Type b Disease**
CLAIRE BROOME, MD

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CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy—In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia. The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527D)

References: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Min Electrolyte Metab 8:237-254, 1982. 2. Danesh BJZ, et al: Comparison between short-term renal haemodynamic effects of propranolol and nadolol in essential hypertension: a cross-over study. Clin Sci 67:243-248, 1984. 3. Hollenberg NK: Introduction: β-adrenergic blocking agents–the treatment of hypertension and the kidney. Royal Soc of Med Int Congress and Symposium Series 51:1-8, 1982. 4. Frohlich ED, et al: Long-term renal hemodynamic effects of nadolol in patients with essential hypertension. Am Heart J 108:1141-1143, 1984. 5. Alexander JC, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

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Since with increasing blood pressure there may be a progressive decline in renal blood flow,[1] prescribe . . .

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Studies prove that CORGARD (nadolol tablets) preserves renal blood flow unlike some beta-blockers, such as propranolol.[1-4]

In a two-year study of 106 patients, CORGARD also decreased serum creatinine, a measurement of improved renal function.[5]

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*For a discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary of prescribing information on adjacent page.

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Dr Matthay is Assistant Professor of Medicine and Anesthesia and Associate Director, Intensive Care Unit, University of California, San Francisco.

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Dr Woeber is Chief of Medicine, Mount Zion Hospital and Medicine Center, and Professor and Vice-Chair, Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco.

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From the Departments of Medicine and Surgery, St Vincent Hospital, Santa Fe, New Mexico. Dr Goldberg is now in practice in Seal Beach, California.

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From the Department of Medicine, University of California, San Francisco, Fresno-Central San Joaquin Valley Medical Education Program and the Medical Service, Pulmonary Section, Veterans Administration Medical Center, Fresno, California. Dr Carbone is now in private practice in Bremerton, Washington, and Dr Stauffer is now at the Milton S. Hershey Medical Center, Pulmonary Division, of the Pennsylvania State University, Hershey, Pennsylvania.

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From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, School of Medicine.

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RICHARD DEAN SMITH, MD
Dr Smith is in private practice in Walnut Creek, California.

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KENNETH W. KIZER, MD, MPH
Dr Kizer is Director, California Department of Health Services, and Assistant Clinical Professor of Medicine, University of California, Davis, School of Medicine.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

November 15-16—**Arizona Chapter, American College of Surgeons.** Loews Ventana Canyon Resort, Tucson. Friday-Saturday. Contact: U of A.

November 16-17—**Review and Update of Gastro-intestinal Pathology.** Scottsdale Hilton, Scottsdale. Saturday-Sunday. Contact: Arizona Society of Pathologists, (602) 246-8901.

November 25-27—**Cemented Versus Uncemented Revision Total Joint Arthroplasty.** Registry Resort, Scottsdale. Monday-Wednesday. Contact: Medical Meetings Department, St. Luke's Medical Center, (602) 251-8402.

December 6-8—**Cardiopulmonary Diseases.** Camelback Inn, Scottsdale. Friday-Sunday. Contact: Department of Radiology, Maricopa Medical Center, (602) 267-5361.

December 7—**Psychiatry.** Tucson. Saturday. Contact: U of A.

February 13-15—**Them Ol' Bones.** Scottsdale Hilton Hotel, Scottsdale. Thursday-Saturday. Contact: St. Luke's Medical Center, (602) 251-8402.

February 21-23—**Anesthesia for the 80's.** Sheraton Scottsdale Resort, Scottsdale. Friday-Sunday. Contact: Arizona Society of Anesthesiologists, (602) 246-8901.

CONTACT INFORMATION

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 95724. (602) 626-6173.

February 24-26—**Emergency Care Update VIII.** University of Arizona, Tucson. Monday-Wednesday. Contact: U of A.

February 24-27—**Practical Radiology: MRI, CT, Intervention, Computers and More.** Loews Ventana Canyon Resort, Tucson. Monday-Thursday. Contact: U of A.

February 26-28—**Ninth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wednesday-Friday. Contact: Phoenix OB/GYN Society, (602) 241-1917.

February 26-March 1—**International Ophthalmic Surgery Symposium.** Loews Paradise Valley Resort, Scottsdale. Wednesday-Saturday. Contact: The Eye Foundation, (602) 257-1077.

February 27-March 1—**Current Issues in Neurology and Neurosurgery.** La Posada Resort, Phoenix. Thursday-Saturday. Contact: Barrow Neurological Institute, (602) 285-3000.

March 6-8—**Focus '86.** Doubletree Inn, Scottsdale. Thursday-Saturday. Contact: St. Luke's Medical Center, (602) 251-8402.

March 8—**Rehabilitation and Aging.** Holiday Inn Broadway, Tucson. Saturday. Contact: U of A.

March 9-11—**Abuses and Controversies in Athletics and Exercise.** Tucson. Sunday-Tuesday. Contact: U of A.

March 18-21—**Pediatric Update 1986.** La Posada Resort, Scottsdale. Tuesday-Friday. Contact: Phoenix Children's Hospital, (602) 239-4350.

March 20-22—**22nd Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thursday-Saturday. Contact: U of A.

March 22-23—**12th Annual James H. McDonald Urological Seminar.** Sheraton Scottsdale Resort, Scottsdale. Saturday-Sunday. Contact: Department of Surgery, Maricopa Medical Center, (602) 267-5371.

March 24-26—**Practical Cardiology for the Family Physician.** La Posada Resort, Scottsdale. Monday-Wednesday. Contact: American College of Cardiology, (301) 897-5400.

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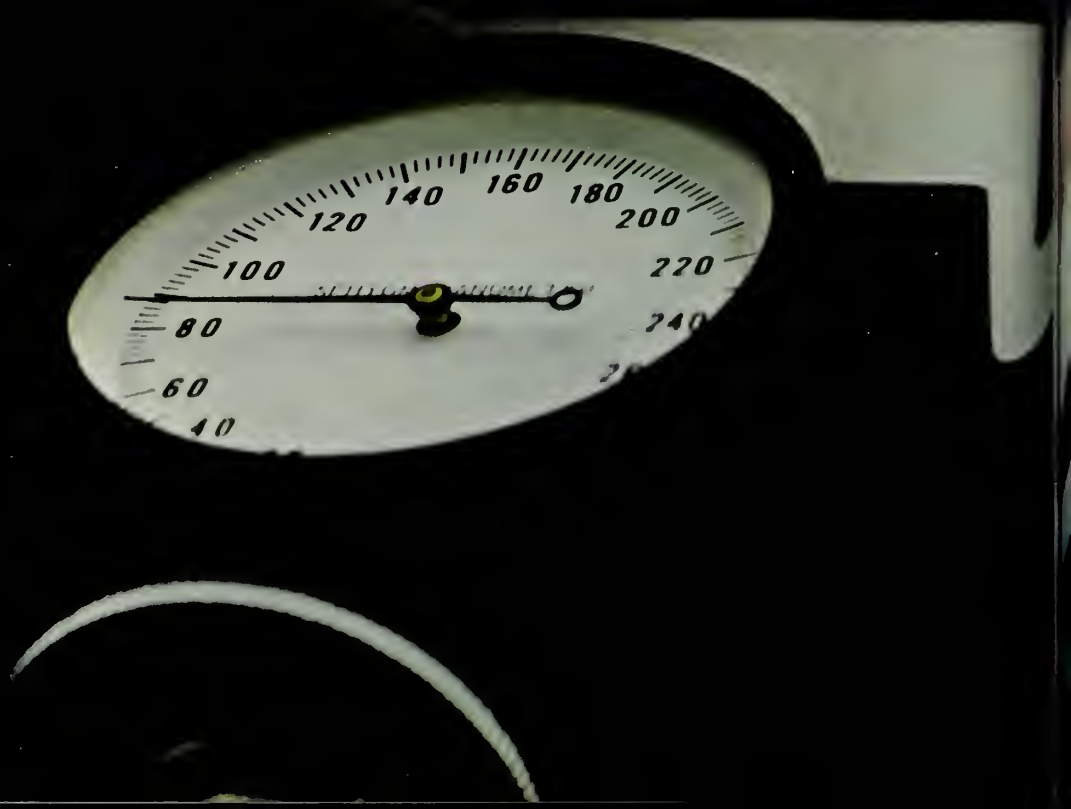

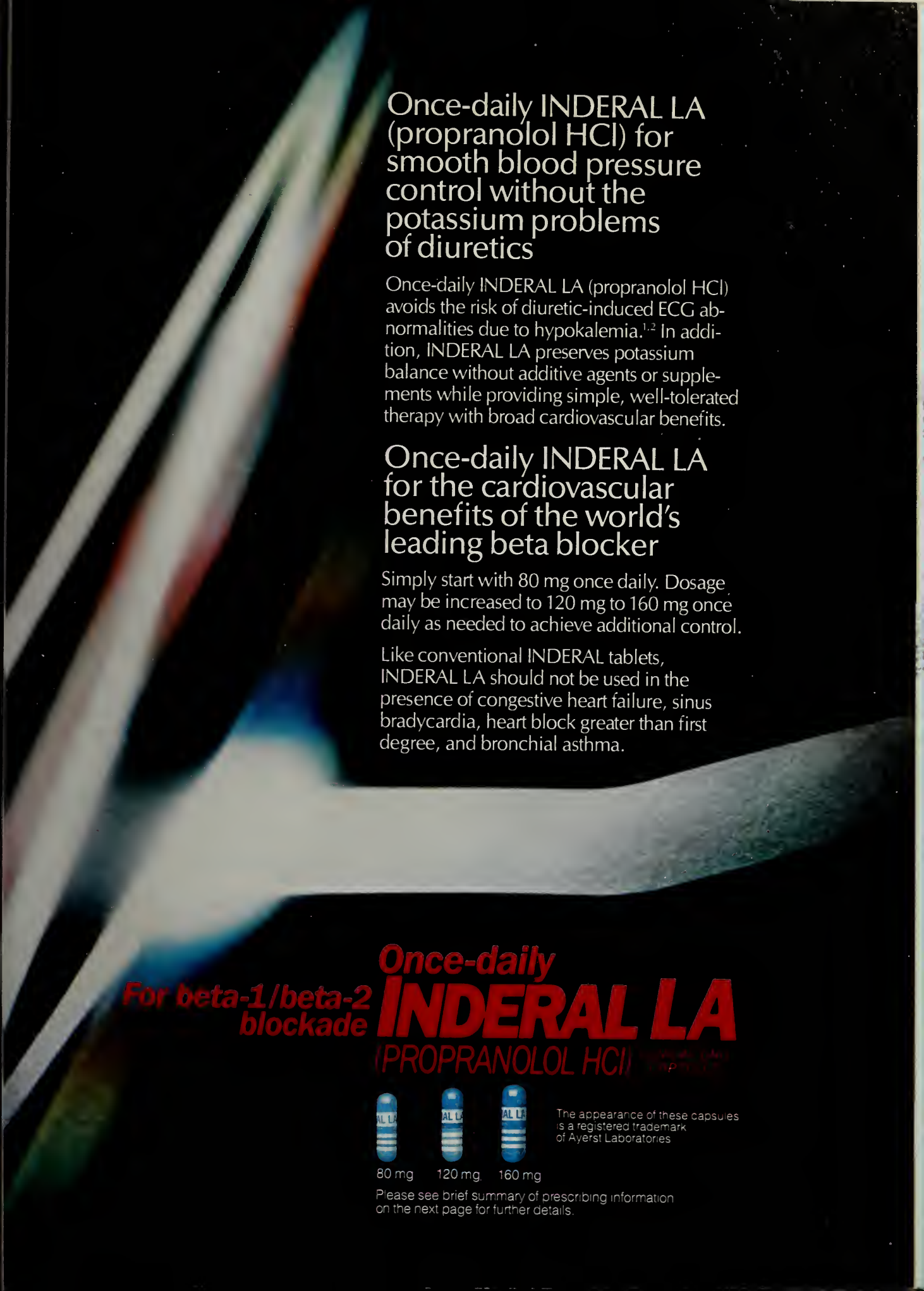

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Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

INDERAL LA

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80 mg 120 mg 160 mg

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Please see brief summary of prescribing information on the next page for further details.

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10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block; hypotension, paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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CALIFORNIA, HAWAII AND NEVADA

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ALLERGY AND IMMUNOLOGY

December 7—**International Symposium of IgG4 and its role in Clinical Immunology.** UC Davis, at Hyatt, Burlingame. Saturday. Contact: Office on Continuing Medical Education, School of Medicine Sacramento. (916) 453-5390.

December 26-30—**Allergy, Drugs, and Drug Allergies.** Symposium Maui, Inc. and Hawaii Medical Association at Hawaii. Thursday-Monday. Contact: Joe Harrison, MD, Program Director Symposium Maui, PO Box 10185, Lahaina, Maui, HI. (808) 879-8182.

January 1-4—**Rheumatology and Immunology.** Symposium Maui, Inc. and Hawaii Medical Association, at Kaanapalo, Hawaii. Wednesday-Saturday. Contact: Joe Harrison, MD, Program Director Symposium Maui, Inc. PO Box 10185, Lahaina, Maui, HI 96761. (808) 879-8182 or 661-8032.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

ANESTHESIOLOGY

January 9-12—**Anesthesia Update 1986.** UCSD at Hotel del Coronado, San Diego. Thursday-Sunday.

January 24-26—**24th Clinical Conference in Pediatric Anesthesiology.** Pediatric and Anesthesiological Foundation and Childrens Hospital at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Wayne Herbert, Program Director, (213) 669-2262.

CANCER

December 11-13—**Second National Symposium on Cellular Oncology.** Memorial Medical Center of Long Beach at Palm Springs. Wednesday-Friday. 16 hrs. Contact: Assistant Director Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach, CA 90801-1428.

CARDIOLOGY

December 2-6—**Chest Radiology Update and Review.** UC at San Diego. Monday-Friday. Contact: Mary J. Ryals, Ryals and Associates, PO Box 610203, DFW Airport, TX 75261-0203. (214) 659-9590.

December 4-7—**Second Annual Seminar and Workshop in Doppler Echocardiography.** UCI at San Francisco. Wednesday-Saturday. 24 hrs. Contact: Kim Stroich, The Institute for Medical Studies, 30131 Town Center Dr., Ste 215, Laguna Nuguel, CA 92677. (714) 495-4499.

December 5-7—**How to Manage Common Cardiac Problems: A Course for the Practicing Physician.** American College of Chest Physicians, at Disneyland Hotel, Anaheim. Thursday-Saturday. 16 hours. $150-$325. Contact: American College of Chest Physicians, (312) 698-2200.

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"Information for Authors"—A complete guide to manuscript submission and journal style is available on request and also appears in January and July.

Author Responsibility—Authors are responsible for all statements, conclusions and methods of presenting subjects. Articles are accepted on condition that they are contributed solely to this journal.

Manuscripts—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

Clinical Investigation—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter.

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Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Because of extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE (piroxicam) at dose of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenital: BUN and creatinine elevations (see PRECAUTIONS)

Body as a Whole: headache, malaise

Special Senses: tinnitus

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

* Reactions occurring in 3% to 9% of patients treated with FELDENE.

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Special Senses: swollen eyes, blurred vision, eye irritations

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis

Dermatologic: onycholysis, loss of hair

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias

Urogenital System: dysuria

Body as a Whole: weakness

Cardiovascular/Respiratory: palpitations, dyspnea

Hypersensitivity: positive ANA

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis: It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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References: 1. Siegmeth W: Serum concentrations of piroxicam in relation to its clinical effect in patients with chronic polyarthritis (trans). *Wien Med Wochenschr* 130:31-35, 1980. 2. Tausch: Placebo-controlled study of piroxicam in the treatment of rheumatoid arthritis. *Am J Med* (report) 72:18-22, February 16, 1982. 3. Buxbaum J, Cronstein B: Efficacy of once daily nonsteroidals in refractory rheumatoid arthritis patients. Presented as a scientific exhibit at the 77th Annual Scientific Assembly of the Southern Medical Association, Baltimore, November 6-9, 1983.

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(Continued from Page 589)

December 6-8—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado at Islandia Hyatt Hotel, San Diego. Friday-Sunday. Fee: $190-$295. Contact: Medical Education Resources, (800) 421-3756.

December 9-10—**Antwerp-La Jolla Research Conference on Cardiac Function: Inotropic Mechanisms and Heart Failure.** UCSD. Monday-Tuesday. 13 hrs. Contact: Karen Delaney, 3960 Park Blvd., Ste F, San Diego, CA 92103 or (619) 692-9115; or PO Box 33185, San Diego, CA 92103.

December 13-15—**Advances in Heart Disease.** American College of Cardiology at San Francisco. Friday-Sunday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

January 30-February 1—**Cardiology 1986: Accomplishments and Expectations.** Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Thursday-Saturday. Contact: Nomi Feldman, 3770 Tansy, San Diego, CA 92138. (619) 453-6222.

EMERGENCY MEDICINE

December 1-6—**Current Concepts in Emergency Care.** Institute for Emergency Medical Education and Washington Chapter of ACEP at Hawaii. Sunday-Friday. 25 hrs. Contact: Group Travel Dept. Kailani World Travel, 4192 Meridian Ave., Bellingham, WA 98227-9951. (800) 426-2561 or WA State (800) 562-2597.

December 9-13—**Postgraduate Institute for Emergency Physicians.** UCSD at La Jolla Village Inn, San Diego. Monday-Friday. 33 hrs. Fee: $215-$440.

January 13-17—**Postgradute Institute for Emergency Physicians, Symposium I.** UCSD at Hanalie Hotel, San Diego. Monday-Friday. 33 hrs. Fee: $215-$440.

January 27-31—**Topics in Emergency Medicine.** UCSF at Holiday Inn, San Francisco. Monday-Friday. Fee: $400.

INTERNAL MEDICINE

January 31-February 1—**4th Annual Recent Advances in Infectious Disease.** UCD at Red Lion Inn. Sacramento. Friday-Saturday.

OB/GYN

November 16—**Review Course for Gynecologic Pathology.** USC at Hilton Hotel, Pasadena. Saturday. Fee: $90. Contact: USC.

December 5-8—**Current Issues in Perinatal Medicine.** Memorial Medical Center at Rancho Mirage. Thursday-Sunday. 14 hrs. Contact: Margaret Frederick, Asst. Dir. Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach, CA 90801-1428.

OPHTHALMOLOGY

January 11—**Blepharoplasty: Cosmetic and Functional Surgery of the Eyelids.** UCLA at Los Angeles. Saturday.

January 17-18—**Advanced Vitrectomy Workshop.** UCLA at Los Angeles. Friday-Saturday.

January 30-February 1—**Lasers in Ophthalmology.** Stanford University at Palo Alto. Thursday-Saturday. 18 hrs.

PEDIATRICS

November 22-25—**Clinical Pediatrics.** American Academy of Pediatrics at Las Vegas. Friday-Monday. Contact: Eve Black, Exec. Sec., PO Box 2134, Inglewood 90305. (213) 757-1198.

December 5-8—**Current Issues in Perinatal Medicine.** Memorial Medical Center of Long Beach at Marriott's Rancho Las Palmas, Rancho Mirage. Thursday-Sunday. 14 hrs. Contact: Margaret Frederick, Center for Health Education, (213) 595-3811.

January 15—**25th Annual Parmelee Memorial Lecture and Neonatal Symposium.** Los Angeles Pediatric Society and California Chapter at Los Angeles. Wednesday. 4 hrs. Fee: $75. Contact: Eve Black, American Academy of Pediatrics, PO Box 2022, Inglewood, CA 90305. (213) 757-1198.

January 25—**Pediatric Victims of Sexual Assault.** UCI at Orange. Saturday.

January 26-29—**11th Annual Winter Ski and Study Symposium.** American Academy of Pediatrics, at Lake Tahoe. Sunday-Wednesday. 10 hrs. Fee: $245. Contact: Eve Black, PO Box 2134, Inglewood, CA 90305. (213) 757-1198.

PSYCHIATRY

November 22-24—**Guided Imagery for Clinicians.** Institute for the Advancement of Human Behavior at Honolulu, Hawaii. Friday-Sunday. Fee: $245-$350. Contact: IAHB, 4370 Alpine Rd., Ste. 205, Portola Valley 94025. (415) 851-8411.

January 26-31—**12th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe. Sunday-Friday. 22 hrs. Fee: $345 before December 15, 1985; $400 after December 15, 1985.

RADIOLOGY

December 2-6—**Chest Radiology Update and Review.** UCSD at San Diego. Monday-Friday. 20 hrs. Fee: $400. Contact: Mary J. Ryals, Ryals and Associates, PO Box 610203, DFW Airport, TX 75261. (214) 659-9590.

January 13-17—**Interventional MRI and Neuroradiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. Fee: $395.

January 31-February 2—**The 38th Annual Midwinter Radiological Conference.** Continuing Education Committee for the Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 19.5 hrs. Contact: Los Angeles Radiological Society, 5200 Century Blvd., Suite 920, Los Angeles, CA. Attn: Diane L. Johnson, (213) 642-0921.

SPORTS MEDICINE

January 19-24—**Sports Medicine: 1986 (A Primary Care Perspective).** UCD at Hyatt lake Tahoe. Sunday-Friday.

SURGERY

November 16—**Lasers on Clinical Medicine and Surgery.** Memorial Medical Center at Long Beach. Saturday. 7 hrs. Contact: Assistant Director Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach, CA 90801-1428.

December 7-8—**Lasers for Facial Aesthetics.** American Academy of Facial Plastic and Reconstructive Surgery at Santa Barbara. Saturday-Sunday. Fee: $325. Contact: Joseph R. Dibartolomeo Ear Foundation, 2420 Castillo St., Santa Barbara, CA 93105. (805) 682-3711.

January 17-18—**8th Annual Surgical Postgraduate Course Catastrophic and Critical Surgical Problems.** UCD at Holiday Inn, Sacramento. Friday-Saturday.

January 20-24—**Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hotel Intercontinental, San Diego. Monday-Friday. 32 hrs.

OF INTEREST TO ALL PHYSICIANS

November 15-17—**Injured Runner Seminar.** UCSD. Friday-Sunday. 19 hrs. Contact: Isabelle S. Green, Camp International Inc., Box 89, Jackson, MI 49204-0089. (517) 787-1600, ext. 291.

November 16—**Systematic Aspects of Chronic Physical Pain.** Mental Research Institute at Palo Alto. Saturday. 5 hrs. Fee: $70. Contact: Training Programs Mental Research Institute, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

November 24—**17th Annual Symposium of Medicine Today.** UCLA at Sheraton Universal Hotel, North Hollywood. Sunday. $100. Contact: Symposium Secretary, (818) 360-1021.

December 6-7—**Clinical Nutrition Update for the Practicing Physician.** UCD at Sacramento. Friday-Saturday. Contact: Office of CME, School of Medicine, UCD, 2701 Stockton Blvd., Sacramento, CA 95817. (916) 453-5390.

December 9-12—**Chest Imaging (Pre) 1986.** UCD at Hotel Del Coronado, San Diego. Monday-Thursday. 24 hrs. Fee: $400.

December 14-21—**Current Concepts in Pain Management.** International Conferences at Hawaii. One Week. 20 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

January 11—**New Applications of Calcium Channel Blockers.** UCSF at The St. Francis Hotel, Union Square. Saturday. Fee: $25.

January 18-25—**Infectious Disease and Toxicological Emergencies.** American Instutite of Postgraduate Education Scripps Memorial Hospital, at Kona Surg Resort, Hawaii. Fee: $350. One week.

January 20-24—**Intensive Course in Geriatric Medicine.** UCLA at Miramar Sheraton, Santa Monica. Monday-Friday. 33 hrs.

January 25-26—**Psychodynamic Group Therapy—1986.** UCLA at Sheraton Grande, Los Angeles. Saturday-Sunday. 13.5 hrs. Fee: $250.

January 26—**MKSAP, Part 1.** UCLA at Los Angeles. Sunday.

January 27-29—**Recent Advances in Geratric Medicine: Transitions in the System of Long Term Care: The State of the Art.** UCSD at San Diego. Monday-Wednesday. Fee: $225.

January 29-31—**9th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn, San Diego. Wednesday-Friday. 21 hrs.

IDAHO

February 1-8—**Sports Medicine.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

(Continued on Page 596)

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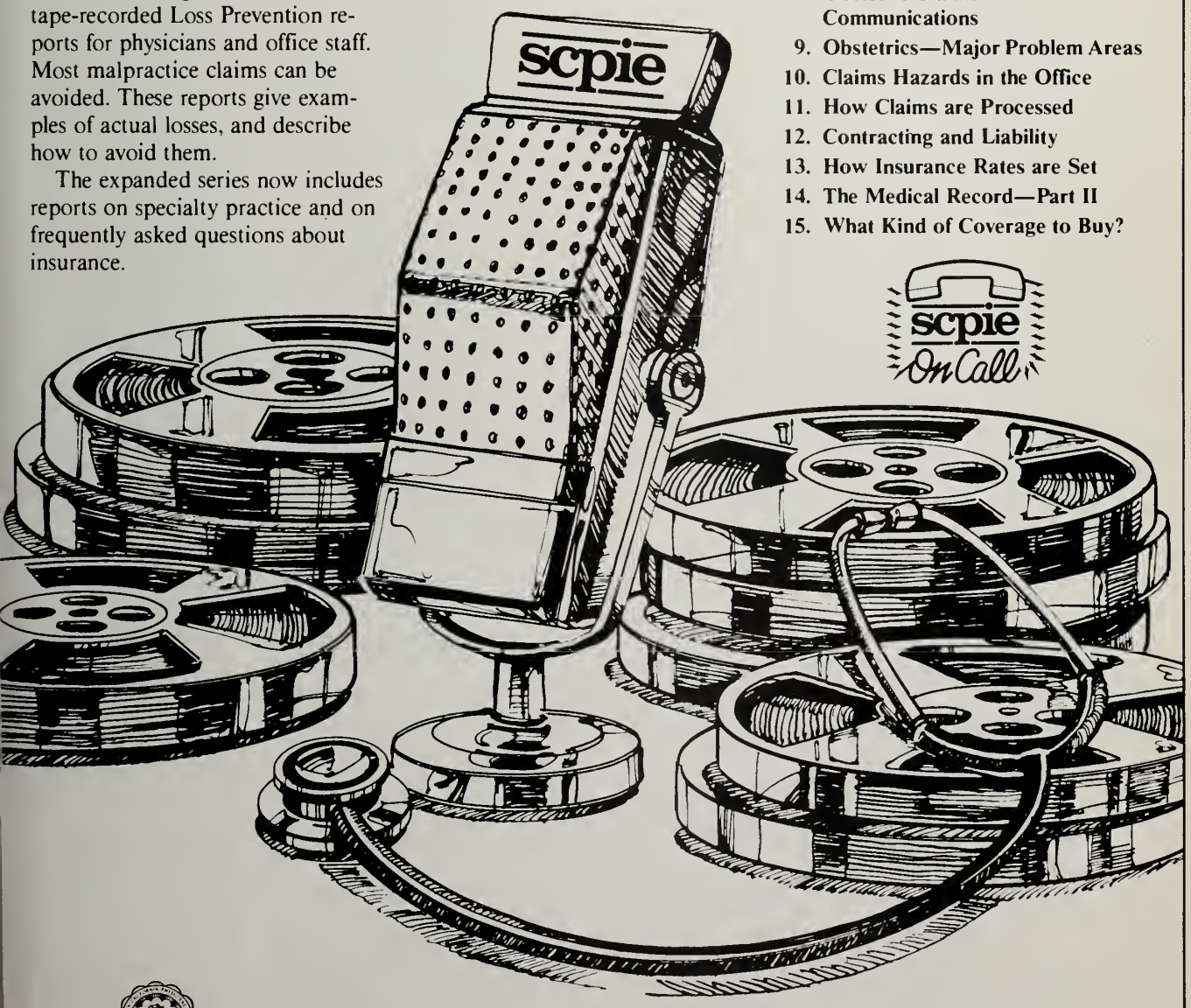

scpie On Call

Sponsored by SOCAP: The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County and Ventura County.

(Continued from Page 594)

February 8-15—**Orthopaedics/Radiology.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 15-22—**Endocrinology/Diabetes.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

MONTANA

See Montana listings under WASHINGTON.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 15-16—**New Mexico Medical Society Interim Meeting—Human Sexuality Update—1985.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. 6 hrs. AMA Cat. I. Contact: NM Medical Society, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

November 22—**Current Concepts on Causes of Cancer.** Los Alamos. Friday. Los Alamos National Labs, Meson Facility. 6 hrs. AMA and NM Cat. I. Contact: Jerry Williams, MD, PO Box 1663, MS-D421, Los Alamos 87545.

November 22-23—**Infectious Disease Update.** Albuquerque. Friday-Saturday. Sheraton Old Town. 10 hrs. AMA Cat. I. Contact: Lovelace Medical Center, Office of CME, 5400 Gibson SE, Albuquerque 87108. (505) 262-7353.

December 5-7—**New Mexico Chapter, American College of Physicians, and New Mexico Society of Internal Medicine**—Annual Meetings. Thursday-Saturday. Marriott Hotel, Albuquerque. 12 hrs. AMA Cat. I. Contact: UNM.

December 13-14—**Trauma Update '85.** Albuquerque. Friday-Saturday. Convention Center. AMA Cat. I. Contact: UNM.

January 25-26—**New Mexico Chapter, American Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 13 hrs. AAFP Prescribed, New Mexico Required Education, Cat. I. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

January 31-February 3—**Murphy's Law in Orthopaedics.** Friday-Monday. Quail Ridge Inn (formerly Tennis Ranch of Taos). 16 hrs. AMA Cat. I and New Mexico Required Education, Cat. I. Contact: Barry Maron, MD, 8324 Constitution Pl. NE, Albuquerque 87110. (505) 292-6062.

February 10-14—**Taos Medical Symposium.** Monday-Friday. Quail Ridge Inn (formerly Tennis Ranch of Taos). 18 hrs, AMA Cat. I, NM Required Education, Cat. I. AAFP Prescribed credit. Contact: Dale A. Gray, MD, 3901 Georgia NE, Albuquerque 87110. (505) 881-6699.

February 14-16—**Second Annual Presbyterian Heart Institute Symposium—Case Studies in Cardiology.** Friday-Sunday. Presbyterian Hospital, Albuquerque. 19 hrs. AMA Cat. I, New Mexico Required Education, Cat. I. Contact: Gilbert Raff, MD, 201 Cedar SE, #604, Albuquerque 87106. (505) 242-2796.

February 20-22—**19th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. Hilton Inn. AMA Cat. I. Contact: UNM.

February 27-March 1—**Second Annual Ruidoso Heart Symposium—Practical Cardiology Update.** Thursday-Saturday. Inn of the Mountain Gods. 16 hrs. AMA Cat. I, NM Required Education, Cat. I. Contact: American Heart Association, NM Affiliate, (505) 268-3711.

March 8—**New Mexico Pediatric Society—Wylder Lecture—Pediatric Allergies.** Saturday. School of Nursing Building, UNM Campus. 4.5 hrs. AMA Cat. I, NM Required Education, Cat. I. Contact: Marilyn Stark, NM Pediatric Association, 7605 Mountain Rd NE, Albuquerque 87110. (505) 265-7431.

CONTACT INFORMATION

UNM—Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

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CONTINUING MEDICAL EDUCATION

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

EMERGENCY MEDICINE

November 14-15—**Symposium on Critical Care Medicine.** Red Lion/Jantzen Beach. Thursday-Friday. Contact: OHSU-CME.

FAMILY PRACTICE

February 10-14—**Family Practice Review.** Portland. Monday-Friday. Red Lion/Lloyd Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

December 4—**Cardiovascular Transdermal Conference.** Portland. Wednesday. Oregon Health Sciences University Library Auditorium. Contact: OHSU-CME.

February 9—**March of Dimes—Sharpening the Focus on Prenatal Care.** Portland. Sunday. Red Lion/Lloyd Center. Contact: OHSU-CME.

February 27-March 2—**Update in Rheumatology.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

(Continued on Page 600)

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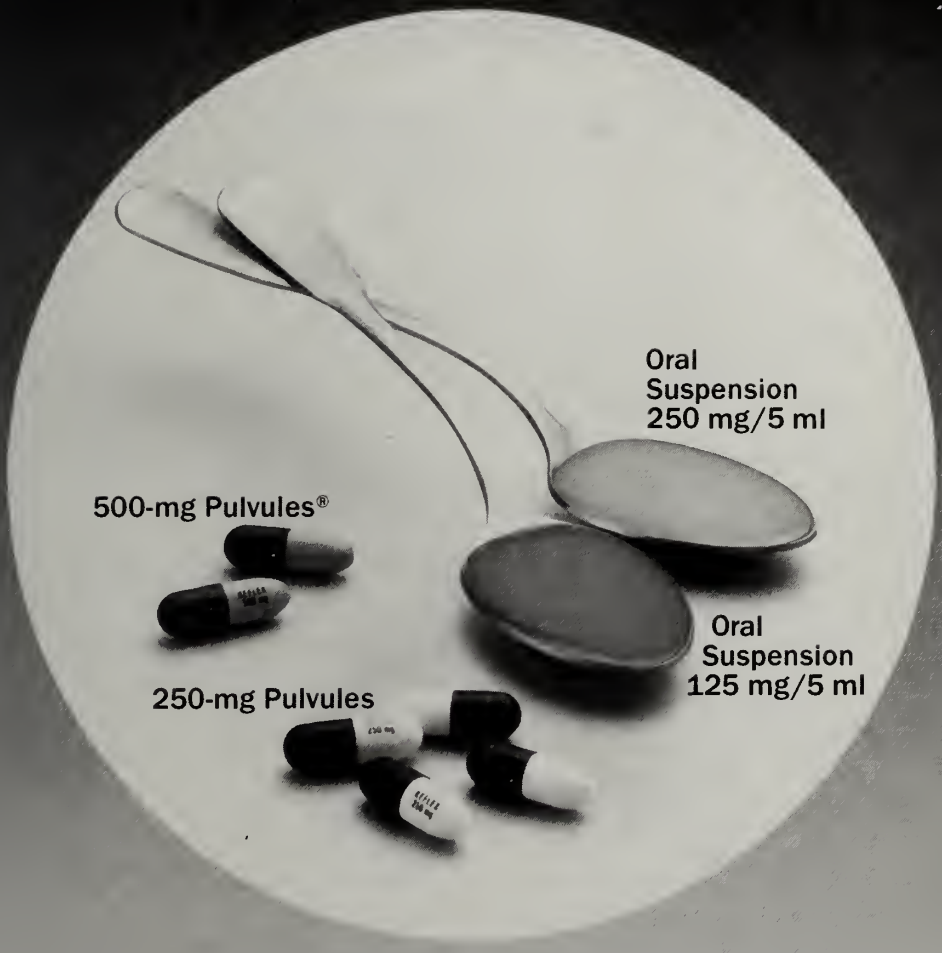

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(Continued from Page 598)

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

November 8-9—**Advanced Trauma Life Support** (Sponsor: University of Utah/Utah Department of Health). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Kim Tanner, (801) 533-6608.

January 20-23—**International Biomedical Engineering Symposium** (Sponsor: University of Utah). Monday-Thursday. Salt Lake City Salt Palace. 18 hrs. Contact: Joseph Andrade, PhD, (801) 581-7236.

April 10-12—**Neurology for the Practitioner** (Sponsor: University of Utah). Thursday-Saturday. Salt Lake City Sheraton. 18 hrs. Contact: J. Richard Baringer, MD, (801) 581-8664.

March 6-7—**Utah Ophthalmological Society Annual Park City Winter Meeting: Corneal Disease** (Sponsors: Utah Ophthalmological Society and University of Utah). Thursday-Friday. Holiday Inn/Yarrow, Park City. Contact: Pam Hanson, (801) 355-5290.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 15—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 15—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 15-16—**Seafood and Health Conference.** Seattle. Friday-Saturday. Seattle Sheraton. Contact: U/W.

November 19—**Common Knee Problems.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

November 21—**Pacific Northwest Endoscopy Society.** Seattle. Thursday. Four Seasons Olympic. Contact: U/W.

November 23-30 (HAWAII)—**Medical Malpractice: Preventive Approach.** Maui. One week. Royal Lahaina. Contact: U/W.

November 26—**Office Dermatology.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

November 29-30—**Syposium on Breast Disease.** Seattle. Friday-Saturday. Seattle Sheraton. Contact: U/W.

(Continued on Page 604)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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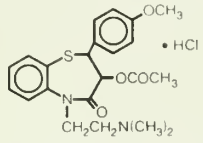

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The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

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In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given, a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks)
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0D88-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0D88-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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(Continued from Page 600)

November 29—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 5-6—**Aging and the Elderly.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

December 6—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 6—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 7—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

December 7-8—**Washington State Society of Anesthesiologists Winter Meeting.** Seattle. Saturday-Sunday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

December 11—**Hypertension.** Seattle. Wednesday. Westin Hotel. Contact: U/W.

December 13—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 17—**Rheumatoid Arthritis—1985.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

December 20—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 27-January 3 (HAWAII)—**Advances in Internal Medicine.** Kauai. One week. Waiohai Hotel. Contact: U/W.

January 3—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 10—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 14—**Osteoporosis: DX and RX.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

January 17—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 17-18—**Advances in Internal Medicine.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

January 21—**Immunization Updates.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

January 22 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

January 23 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

January 23-24—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

January 24-25—**Eye Care for Primary MDs.** Seattle. Friday-Saturday. Westin. Contact: U/W.

January 24—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 24 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

January 30-31—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

January 31—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 1-8 (IDAHO)—**Sports Medicine.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 6-7—**Neurology Update.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

February 7—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 7-8—**Clinical Problems in Urology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 8-15 (IDAHO)—**Radiology.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 14—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 15-22 (IDAHO)—**Endocrinology/Diabetes.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 18—**Antiviral Strategies.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

February 19 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Columbus Hospital. Contact: U/W.

February 20 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

February 20-22 (HAWAII)—**Father Damien's Colony.** Molokai. Thursday-Saturday. Sheraton Molokai. Contact: U/W.

February 21—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 21 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

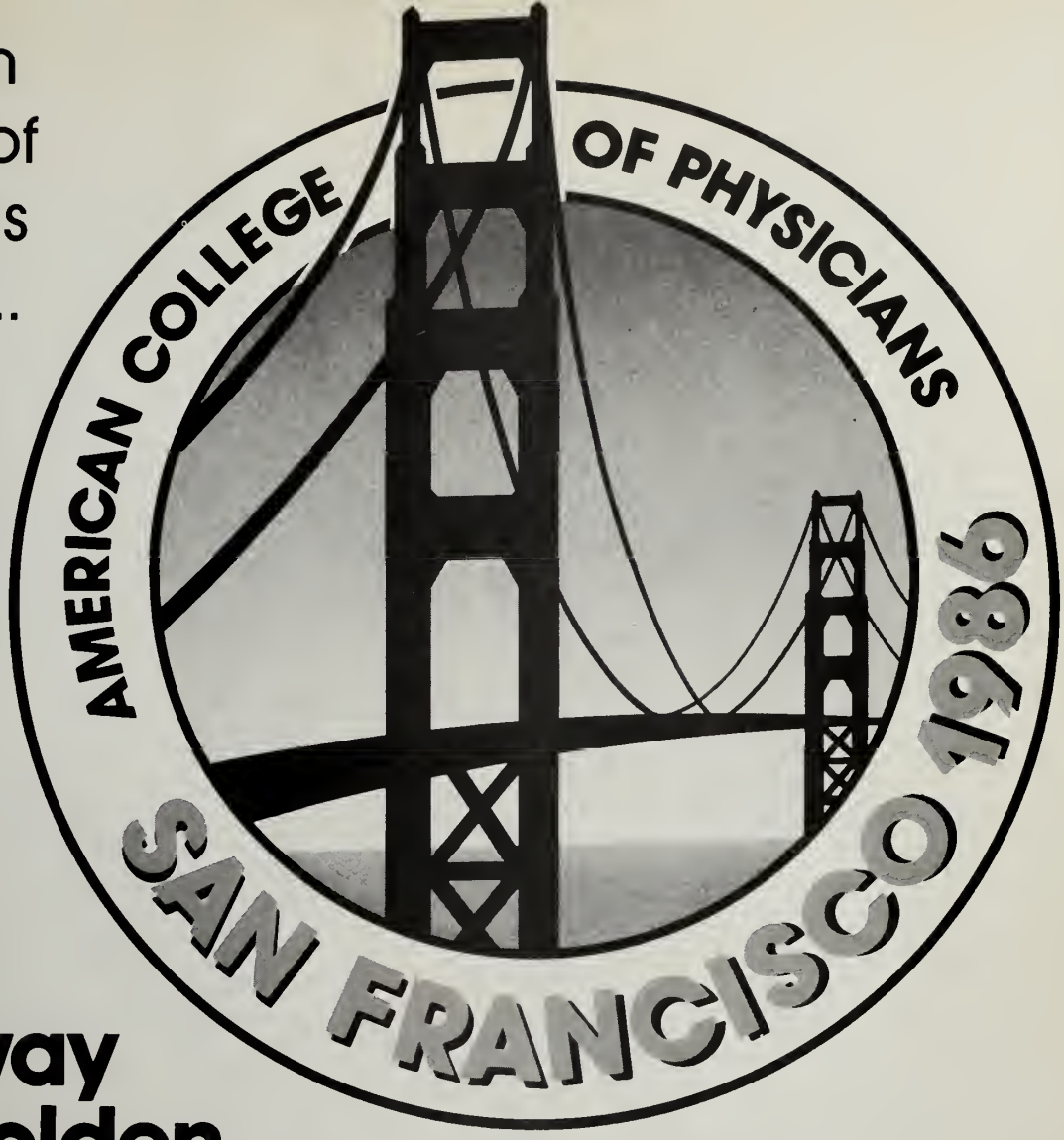
February 23-March 1 (HAWAII)—**Trauma/Surgery.** Kona. Sunday-Saturday. Royal Waikoloa. Contact: U/W.

February 25—**Child Rearing Practices.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

February 28—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

(Continued on Page 608)

American College of Physicians presents...



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Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis. Relief of mild to moderate pain and primary dysmenorrhea. Safety and efficacy in children are not established.

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with MOTRIN.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

MOTRIN can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, blurred vision, skin rash, weight gain, or edema. Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (eg, eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Drug interactions—*Aspirin:* used concomitantly may decrease MOTRIN blood levels.
Coumarin: bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal, of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater Than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence Less Than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence Less Than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis, cataracts; **Hematologic:** Bleeding episodes (eg, epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction, acidosis; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **Renal:** Renal papillary necrosis.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Do not exceed 3200 mg/day.

Rheumatoid arthritis and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

How Supplied:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
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Unit-dose package of 100	Unit-dose package of 100	Bottles of 500
Unit of Use bottles of 100	Unit of Use bottles of 100	

Caution: Federal law prohibits dispensing without prescription. *For additional product information, see your Upjohn representative or consult the package insert.*

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

MED B-8-S
June 1985
J-5503

CONTINUING MEDICAL EDUCATION

(Continued from Page 604)

February 28-March 1—**Neurology—Past, Present, Future.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

March 7—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 14—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 15-22 (HAWAII)—**Death Investigation.** Maui. One week. Royal Lahaina. Contact: U/W.

March 15-22 (HAWAII)—**Advanced Cardiac Life Support.** Kauai. One week. Kauai Sheraton. Contact: U/W.

March 18—**Shoulder Injuries.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 19 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

March 20 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

March 21 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

March 21—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 21-22—**Medicine for Psychotherapists.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

March 22—**Radiology Northwest.** Seattle. Saturday. UW Health Sciences Building. Contact: U/W.

March 22-29 (HAWAII)—**Ortho/OBGYN/Pain/Obesity/Surgery.** Kauai. One week. Kauai Sheraton. Contact: U/W.

March 25—**What's New In Imaging.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 28—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 3-4—**Oncology.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

April 4—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 5—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 5-12 (HAWAII)—**Drug Therapy.** Kauai. One week. Sheraton Princeville. Contact: U/W.

April 7-18—**Rehab Medicine Review.** Seattle. Monday-Friday. Seattle Sheraton. Contact: U/W.

April 11—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 15—**Reflux and Surgery.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 16 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Columbus Hospital. Contact: U/W.

April 17 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

April 18—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 18 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

April 22—**Common Knee Strains/Sprains.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

April 25—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 1-5—**Psychomotor Skill.** Seattle. Thursday-Monday. Westin Hotel. Contact: U/W.

May 2—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 2-3—**Functional Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8-9—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

May 9—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 16—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 20—**Hyperlipidemias.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 21 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

May 22 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

May 23 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

May 23—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

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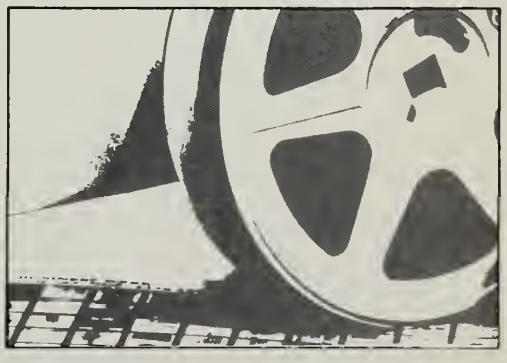

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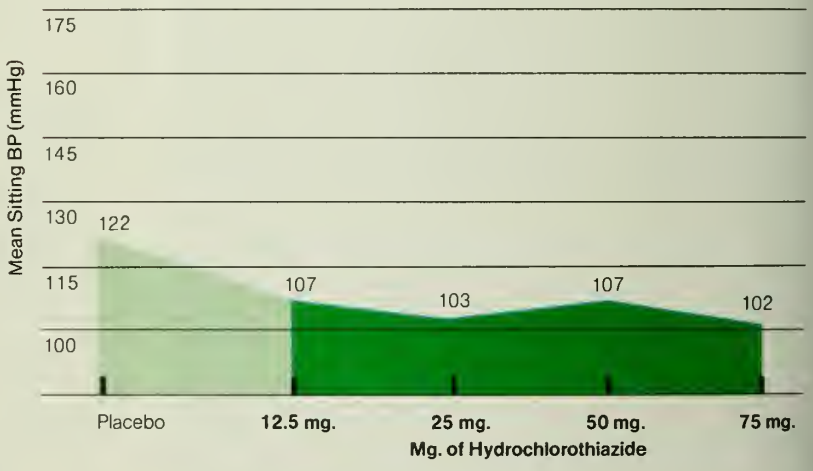

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Marshall B. Block, M.D.
Editor

"THE BUCK STOPS HERE"

Physicians are, and will be, the final common path through which medical care is received. The public, as patients, interact with us and see us as the controlling force in their health care. Their employer, their insurance company, their insurance agent, or the group within which the physician works, are all nebulous impersonal organizations which have no bearing to them. Thus, the major decisions which are now being forged in the health care delivery system at federal, state, and local levels will be perceived by patients in their interaction with their physician. We therefore need to look carefully at this relationship in order to understand its dynamics.

A physician-patient relationship is unique and at the same time extremely complex. From the physician point of view, patients represent the ability to practice one's training and at the same time generate a source of income to help support the physician's practice and personal needs. The relationships which form between patient and physician also bolster the physician's self-confidence and self-esteem, which in turn can lead to enhancement of the initial values noted above. Inherent in this scenario is the physician's allegiance to the patient and his desire to improve the plight of the patient, whether it be medical, social or psychological. In essence, the physician is the patient advocate, and in so performing this function he receives financial, social and psychological rewards.

Patients choose physicians for complex reasons. Obviously, most choose a physician because of his medical expertise, but, on the other hand, there are some patients who choose physicians because of personality factors regardless of their medical competence. In between, the vast majority of physicians and patients find a happy compromise. Inherent in the fee-for-service relationship is the patient's ability to sever a relationship if they feel that they are not getting a fair return on their investment. It is therefore not without surprise that many physicians, especially early in their practice lives, feel a sudden pang of sadness and introspection whenever a "Please transfer my medical records" slip arrives at their office. In an attempt to please patients and thus gender a "good relationship" so that the patient will continue to return for ongoing medical care, the physician feels that he has failed when a patient decides to choose another physician. The patient, however, considers the phys-ician a "stranger," even though the patient has shared many intimate details of his or her life with the practitioner. Severing a relationship is thus easier than when the "friendship" is on a nonprofessional level. In essence, the patient ultimately has had the controlling hand in determining whether a relationship with a physician was to prosper.

Thus, the motivation and perception of physicians and patients are entirely different in the fee-for-service environment, but this may change with the alterations occurring in the delivery of health care. The patient will no longer have free rein in choosing a practitioner. Rather, the medical plan within which he finds himself will probably give him a limited number of choices. This will remove, somewhat, the controlling influence the patient has on the physician-patient relationship. Physicians, on the other hand, will also have a changing motivational pattern within this new system. Although the underlying desire to provide good medical care will hopefully remain, the source of professional and financial rewards will undergo a metamorphosis. The desire to "please" will not be as keen, for the physician will recognize that the patient is "locked-in" and no longer has the ability to make lateral shifts so rapidly. This no doubt will lead to less intense physician-patient relationships. If all this were not enough, physicians are becoming involved in ownership positions in many of these health care delivery plans, which will pose added burdens on their patient relationships. The burgeoning attempt to ration medical care is an anathema in our society, and the politicians who are attempting to manipulate the system to accomplish this goal do not want to be seen as the instigators of this new wave, for it would be political suicide. They will attempt to transfer decision-making to the people who "know best," ourselves. We will become the arbitragers of supply and demand in the marketplace, and unless we are very careful, we may become the "fall guys" for the multiple influences now in the marketplace affecting the quality and quantity of health care services that are and will be available. For instance, there are independent practice associations and preferred provider organizations which are being developed in such a manner that a gatekeeper will be in personal financial jeopardy if medical services exceeding a certain predetermined amount are utilized. In this kind of setting, it is easy to understand how difficult it would be for a physician to function as a patient advocate if, when having to make complex medical decisions, he would also have to consider if he will be personally financially at risk for these decisions. Avoiding situations like this can go a long way to eliminating such a conflict. By establishing committees at each hospital composed of medical, religious and legal personalities, ethical and moral decisions could be shouldered by a number of persons in addition to ourselves making some of these issues easier to handle. Being alert to these pitfalls now, and taking appropriate action will enable us to continue our historical role as the patient advocate.

Marshall B. Block, M.D., Editor

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Cardiovascular Risk Factor Assessment In Phoenix Physicians — I. Risk Factor Variables

Abstract

Cardiovascular disease mortality, though still the major cause of disease-related death, is on the decline. The principal reasons given for this drop are improved therapeutic methods and increased awareness and application of preventive measures. It has been hypothesized that physicians should have a lower cardiovascular risk factor profile than the general population due to their access to these risk-lowering methods.

To examine this theory, we invited over 3200 Phoenix-area physicians to participate in a free, confidential cardiovascular risk factor assessment. Five hundred and sixteen (473 males, 43 females) ranging in age from 27 to 83 years (means 49.1) elected to take part in the study.

We found that female physicians had lower mean cholesterol (203.4 mg/dl) and triglycerides (87.0 mg/dl) than their male counterparts (208.6 mg/dl) and 119.6 mg/dl, respectively), while their HDL-cholesterol concentrations were significantly higher (60.7 mg/dl vs. 49.7 mg/dl for males, p=0.001). Of the male physicians, 4.7% had blood pressure readings in excess of 160/95 mmHg, and 15.5% had cholesterol levels above 250 mg/dl.

Nearly a quarter of the physicians had cholesterol values above the moderate risk level published by the Council on Scientific Affairs' Consensus Conference (1985). The 10.3% of male physicians who were current cigarette smokers had significantly higher mean total cholesterol levels and mean total to HDL-cholesterol ratios than nonsmokers (221 mg/dl vs. 207 mg/dl, p=0.025; 5.1 vs. 4.4, p=0.007, respectively). Their mean HDL-cholesterol level was lower (45.3 mg/dl vs. 60.2 mg/dl for nonsmokers, p=0.019), and they also had a higher prevalence of hypertension (17% vs. 13%).

While Phoenix physicians paralleled the nationwide trend toward lower physician smoking rates than the general population, those who did smoke had twice the six-year probability of developing coronary artery disease (6.7 compared to 3.6 for nonsmokers) according to the Framingham Risk Factor Probability Tables. We conclude from this assessment that physicians have an unfavorable cholesterol profile in light of recent recommendations, and physician-smokers manifest an especially high coronary disease risk probability.

Introduction

Coronary artery disease continues to play a major role in morbidity and mortality in the American population. Beginning with the Framingham Heart Study,[1] the last three decades have led to the recognition and acceptance of the concept of risk factors for coronary artery disease. Both public and physician awareness of the role of risk factors has been a goal of the health professions. Improvement in the coronary artery disease risk factor status of the American population has been documented[2] and proposed as the principal explanation for the decline in cardiovascualr mortality in the last fifteen years.[3]

Physicians as a group are thought to have a lower coronary artery disease risk factor profile than the population in general. Various surveys have documented the specific cigarette smoking habits of physicians.[4-10] However, an overall risk factor assessment of physicians has not been reported. The Arizona Heart Institute and St. Joseph's Hospital and Medical Center undertook jointly in 1983 a study to document the coronary artery disease risk factor status of the physician community in the greater Phoenix area.

Materials and Methods

A letter of invitation to participate in the study was sent to all physicians living in the greater metropolitan Phoenix area (Maricopa County) and listed on the rolls of the state medical society. The approximately 3200 physicians were encouraged to take advantage of the no-cost cardiovascular risk factor assessment, with confidentiality being assured to the participants.

The examinations were conducted at the Arizona Heart Institute. The physicians were asked to complete a cardiovascular questionnaire to document any personal or family history of cardiac, vascular, or cerebrovascular disease or symptoms. Several questions on lifestyle habits (smoking, exercise, dietary restrictions, and Type A or B personality pattern) were also posed to the participants. Height, weight, and frame size were then measured and recorded. Fasting blood samples were drawn for determination of blood lipids and glucose. A routine cardiovascular physical examination was then done, and sitting pulse rate and blood pressure readings were taken. Physicians without contraindications were given a maximal treadmill test using the Bruce protocol.

Analyses of the blood samples were performed by the Clinical Laboratory at St. Joseph's Hospital and Medical Center. Total cholesterol and glucose levels were determined by the Technicon enzymatic method (SMAC-20); HDL-cholesterol and triglyceride evaluations were run on the DuPont ACA Clinical Analyzer using standard procedures.

Statistical manipulations of the data were carried out on a Texas Instrument Professional Computer using SYSTAT software. Intergroup comparisons were analyzed using non-paired t-tests for unequal group size.

From the Departments of Cardiovascular Surgery (Dr. Diethrich) and Preventive Medicine (Dr. Smith), Arizona Heart Institute, Phoenix, Arizona. Reprint requests to: Edward B. Diethrich, M.D., Arizona Heart Institute, P.O. Box 10,000, Phoenix, Arizona 85064.

Results

A total of 516 physicians took part in the heart disease risk assessment. There were 473 men and 43 women; ages ranged from 27 to 83 years with a mean age of 49.1 years.

Twenty subjects (3.9%; 15 males, 5 females) reported a history of myocardial infarction, twelve of which had occurred under age 60. Thirteen percent indicated they had hypertension, and 5% said they were hypercholesterolemic. None of the participants reported symptoms of cerebrovascular disorders.

Fifty-six percent of the males and 65% of the females rated themselves as having Type A behavior pattern, and only 30% of all physicians indicated that they engaged in regular aerobic exercise (30 minute sessions at least 3 times weekly). The body mass index for males ranged from 17-36 (mean: 24.9) and from 18-34 (mean: 23.4) for women, indicating that the group as a whole was not overweight. The percentage of subjects admitting to current cigarette smoking was 10.3 for men and 4.7 for women.

Table 1
Risk Factor Variables for Phoenix Physician Cohort, Males vs. Females

Risk Variables	Males (n=473)	Females (n=43)
Age	range: 28-83 mean: 49.4±13.2*	range: 27-78 mean:46.1±12.0*
Body Mass	range: 17-36 mean: 24.9±3.0	range: 18-34 mean: 23.4±3.4
Type A Personality	56%	65%
Current Cigarette Smoking	10.3%	4.7%
Total Serum Cholesterol (mg/dl)	208.6±40.7	203.4±36.9
HDL-cholesterol (mg/dl)	49.7±13.1	60.7±15.9
Total/HDL-cholesterol	4.5±1.6	3.6±1.2
Triglycerides (mg/dl)	119.6±86.3	87.0±56.8
Blood Glucose (mg/dl)	96.0±18.0	90.9±9.7
Systolic Blood Pressure (mmHg)	123.1±16.8	112.2±16.4
Diastolic Blood Pressure (mmHg)	77.8±9.8	71.8±10.7

*mean ±1 SD

Table 1 compares the mean and standard deviations for the various subjective and objective risk factor variables between males and females in the study. The women enjoyed only a slightly lower total cholesterol level (203.4 mg/dl vs. 208.9 mg/dl for males), but they had significantly higher mean HDL-cholesterol concentrations (60.7 mg/dl vs. 49.7 mg/dl, p=0.001) and therefore a lower ratio of total cholesterol to HDL-cholesterol (mean 3.6 for women compared to 4.5 for males, p=0.001). Women also displayed lower triglyceride levels (mean value of 119.7 mg/dl for males, 87.0 mg/dl for females, p=0.018) and blood pressure readings (means of 123.1/77.8 mmHg for males, 112.2/71.8 mmHg for females, p=0.001 for both systolic and diastolic readings).

Inasmuch as over 90% of the participants in the study were males, the data on females was excluded from further scrutiny and comparisons at this point, and only the three major heart disease risk factors: smoking, blood lipids, and blood pressure, were further examined. Table 2 breaks down these risk variables in the male participants according to age-decade. The mean cholesterol and triglyceride levels rose steadily until the fifth decade and then began to fall. Of interest was the bimodal distribution of the percentage of male smokers. The highest proportion of current smokers (12.5%) was reported by physicians in the fourth and eighth decades; no one under the age of 30 admitted to smoking, but the number in this category was small (11 subjects).

Table 3 presents the three risk factor variables according to specialty for 433 of the male physicians; 40 subjects were excluded for lack of specialization reporting on their questionnaires. The proportion of physicians by specialty in this study parallels fairly well their numbers in the overall physician population in Maricopa County. That is to say, 26% of the physicians in the county are listed under the surgical specialties (including OB/GYN); 30% of the participants in this study were surgeons. The medical specialists (including anesthesiologists) accounted for 58% of the physicians in the county and 51% of the study population. Sixteen percent of the county's physicians are generalists; 19% of the study group was comprised of general physicians.

The physicians in the medical specialties exhibited the lowest total cholesterol, HDL-cholesterol, and total to HDL-cholesterol ratio in the study. They also had the fewest smokers (7%), compared to surgeons with twice the rate (14.8%). There was no significant difference in the blood pressure readings among the three categories.

To give perspective and clinical significance to the three risk factor variables, Table 4 summarizes the percentages of the 473 male physicians with risk factor levels equal to or above standard clinical reference norms for blood pressure and cholesterol. The divisions were assigned arbitrarily to reflect commonly used values in clinical assessment. A diastolic blood pressure greater than 90 mmHg was found in 13.4% of the physicians, while 15.3% had a systolic pressure above 140 mmHg. If we use the World Health Organization definition of hypertension as pressures equal to or greater than 160/95 mmHg, 4.7% of the male physicians were hypertensive.

In terms of blood lipids, 15.5% of the male physician cohort demonstrated a total serum cholesterol in excess of 250 mg/dl, the level heretofore commonly associated with mild hypercholesterolemia in middle-aged males. Only 1.9% of this group had a level above 300 mg/dl.

Table 2
Phoenix Male Physician Risk Variables by Age

Age (n)	Lipids				Blood Pressure		Smokers
	CHOL	HDL	CHOL/HDL	TRGL	SYST	DIAST	%
<30 (11)	177±32	47.4±12	4.0±1.4	103±80	119±20	79±16	0.0
30-39 (115)	197±38	49.4±13	4.3±2.1	106±89	118±12	76±9	12.5
40-49 (140)	204±41	49.1±12	4.4±1.6	119±85	120±15	78±9	8.5
50-59 (98)	226±42	49.9±13	4.8±1.7	136±103	124±16	79±9	9.5
60-60 (61)	219±38	50.6±14	4.6±1.2	123±68	129±18	79±10	11.5
≥70 (48)	208±35	49.7±14	4.5±1.2	125±63	137±22	77±11	12.5

CHOL: total serum cholesterol in mg/dl
HDL: HDL-cholesterol in mg/dl
CHOL/HDL: total to HDL cholesterol ratio
TRGL: triglycerides in mg/dl
SYST: systolic pressure in mmHg
DIAST: diastolic pressure in mmHg
Lipid and blood pressure values are mean ±1 SD

Table 3
Risk Factor Variables of Male Physicians by Specialty

Variable*	Specialty*		
	Medical (n=216)	Surgical (n=126)	General (n=81)
Age	46.9±11.9	47.7±11.1	49.9±13.3
Total Cholesterol	205.1±37.6	211.0±45.5	209.3±39.5
HDL-cholesterol	50.4±13.8	48.7±11.9	48.4±13.1
Total/HDL-cholesterol	4.4±1.8	4.6±1.6	4.6±1.4
Triglycerides	120.1±95.7	112.8±73.0	130.8±92.6
Systolic Pressure	121.0±15.3	122.0±16.1	123.6±16.2
Diastolic Pressure	78.1±9.9	77.2±9.6	77.4±9.5
Smokers	7.0%	14.8%	11.3%

*mean ±1 SD unless otherwise noted
lipid values are in mg/dl
blood pressure figures are in mmHg

However, when the data was compared with the newer, more stringent recommendations of NIH's Consensus Development Conference on lowering blood cholesterol,[11] the risk factor values took on more ominous significance. In the fourth decade category, for example, 28.6% of the population was at moderate risk, with another 14.3% rising into the high risk level. Similar percentages were seen in the fifth and above decades.

According to the Framingham Heart Study data,[1] a total to HDL-cholesterol ratio of 4.9 or above corresponds to an "average" risk level. The rate of physicians in this study with a ratio above 5.0 was 31.8%; only 2.5%

had a ratio higher than 7.5

To better appreciate any association between cigarette smoking and the other two major risk factors, we compared physician smokers to nonsmokers in terms of mean values for cholesterol, HDL-cholesterol, and the total to HDL-cholesterol ratio (Table 5). The smokers had significantly higher ($p=0.025$) cholesterol levels (221 mg/dl for smokers compared to 207 mg/dl for nonsmokers); they also had lower HDL-cholesterol levels (45.3 mg/dl vs. 50.2 mg/dl, $p=0.019$) and higher ratios (5.1 vs. 4.4, significant at the $p=0.007$ level). In terms of percentages of physicians with moderate risk levels (as defined in Table 4), 23% of the physician-smokers had a total cholesterol level in excess of 250 mg/dl; only 14% of nonsmoking physicians were above this level. In addition, hypertensive blood pressure readings were more prevalent in the smokers (17% compared to 13% for a diastolic reading above 90 mmHg, $p<0.05$).

Results of the maximal treadmill testing and further evaluation on the physicians will be presented in Part II of this report.

Table 4
Levels of Risk for Male Physicians: Percentage with Risk Factors Equal to or Above Clinical Reference Values

Blood Pressure (mmHg)		
Diastolic Pressure	≥90	13.4%
Diastolic Pressure	≥95	4.7%
Diastolic Pressure	≥100	2.3%
Systolic Pressure	≥140	15.3%
Systolic Pressure	≥160	4.7%
Blood Lipids (mg/dl)		
Total Cholesterol	≥250	15.5%
Total Cholesterol	≥300	1.9%
Total Cholesterol by Age:		
20-29 years	≥200	18.2% (moderate risk)
	≥220	9.1% (high risk)
30-39 years	≥220	28.6%
	≥240	14.3%
over 40 years	≥240	24.7%
	≥260	14.0%

Table 5
Comparison of Other Risk Factors Between Physician-Smokers and Nonsmokers

Variable	Smokers	Nonsmokers	P
Mean Total Cholesterol	221	207	0.025
Mean HDL-cholesterol	45.3	50.2	0.019
Mean Total/HDL-cholesterol	5.1	4.4	0.007
Total Cholesterol ≥250	23%	14%	<0.05
Total/HDL-cholesterol ≥5.0	50%	30%	NS
Diastolic Pressure ≥90	17%	13%	<0.05
Systolic Pressure ≥140	19%	15%	<0.05

lipid values in mg/dl
blood pressure figures in mmHg

Discussion

The concept of risk factors and coronary artery disease prevention has gained an increasing role in the health habits and medical care delivery in this country. Several studies of cardiac risk factors have documented the profiles of various groups in the United States population. Moreover, one health hazard in particular, smoking, has been examined specifically in several physician populations,[4-10] but we are unaware of any attempt to profile the cardiovascular disease risk potential of a group of physicians to ascertain how they compare to the population in general. We undertook the investigation of the heart disease risk factor status of physicians in a large metropolitan area.

Although the 516 physicians in our Phoenix Physicians' Risk Factor Evaluation represented only 16% of the target group, their age, sex, and specialty distributions fairly well paralleled those in the entire physician population of the greater Phoenix area. While no racial data was included in the study, more than 95% of the participating physicians were Caucasians, again an accurate reflection of the target population. This racial hemogeneity allowed us to compare our study results with those other pouplations similarly evaluated for coronary artery disease risk.

For purposes of these comparisons, we chose to use only those risk variables which could be objectively measured; the notable exception being a history of smoking. Our data was not sufficiently detailed to allow adequate analysis of personality type, nutritional status, or exercise habits, and because our group was on average not overweight, the question of obesity was not a factor. Personal and family disease histories were likewise excluded from comparison, leaving blood lipids, blood pressure, and smoking as the three major risk variables suitable for analysis.

Of the several large population studies of heart disease risk, probably the Framingham Heart Study is the most widely known. Since the original data is over three decades old, it is not sufficiently current enough to apply to our physician group. However, the Framingham Offspring Study (FOS),[12] completed in 1971, offers a bet-

ter source of age-matched, predominantly Caucasion subjects. If we look at just the 30-49 age group, we find that the Phoenix cohort had significantly lower average systolic and diastolic blood pressure readings (118-120/75-77 mmHg for the Phoenix physicians; 125-131/81-86 mmHg for the FOS group, $p<0.05$). However, the range of cholesterol levels was much closer: 197-204 for the physicians and 197-200 for the FOS group.

Even more current is the data from the newly published Minnesota Heart Study (MHS).[13] This project sampled 4000 largely urban whites between 1980 and 1982, 88% of whom had completed at least high school. Although the population did not correlate well on the economic level (only 17% of the MHS cohort had annual incomes above $40,000), there was sufficient similarity for comparison. As Table 6 shows, the males in the two studies had parallel values for systolic and diastolic blood pressure readings and cholesterol. Only HDL-cholesterol concentrations were consistently higher in the Phoenix population throughout the age strata.

Table 6
Comparisons of Minnesota Heart Study[13] and Phoenix Physicians' Risk Factor Evaluation Variables by Age

Variable	Age Groups			
	25-34	**35-44**	**45-54**	**55-64**
Minnesota Sample Size	507	398	309	247
Phoenix Sample Size	59	144	116	69
Systolic Pressure				
Minnesota	120±11	122±13	124±14	130±16
Phoenix	117±11	120±15	120±15	127±16
Diastolic Pressure				
Minnesota	72±11	77±11	78±11	79±10
Phoenix	76±10	78±9	77±9	79±9
Total Cholesterol				
Minnesota	184±34	208±42	215±36	218±39
Phoenix	192±40	200±40	215±41	221±43
HDL-cholesterol				
Minnesota	44±12	43±12	43±12	42±11
Phoenix	51±15	49±13	48±11	50±11

The most consanguineous data for comparison comes from a 1978 report on physician-runners who entered the 1977 Boston Marathon.[14] The 50 marathoners and the 43 matched controls, all physicians, were also similar in average age, race, and gender to our cohort (only one female in each of the two groups, runners and controls). Table 7 compares the three groups. The Phoenix physicians were nearly equivalent to the nonmarathoning physicians, but had a potentially more favorable DHL-cholesteral level. However, the Phoenix group could not compare favorably with the lower triglyceride and diastolic blood pressure levels of the marathoning physicians, none of whom smoked. The marathoners also had significantly higher HDL-cholesterol concentrations.

Table 7
Phoenix Physician Subgroup Comparison with Marathon and Nonmarathon Physicians[14]

Variable	Phoenix Physicians (144 males 35-44 yr.)	Marathoners (49 males 1 female ave. age 40)	Non-marathoners (42 males 1 female Ave. age 43)
Systolic Pressure	120±15	117±11 (NS)*	120±8 (NS)
Diastolic Pressure	78±9	72±2 (0.01)	75±9 (NS)
Total Cholesterol	200±40	194±31 (NS)	200±37 (NS)
HDL-cholesterol	49±12	54±14 (0.03)	45±9 (0.03)
Total/HDL-cholesterol	4.4±1.6	3.8±1.1 (NS)	4.6±1.3 (NS)
Triglycerides	119±85	85±75 (0.01)	89±49 (0.01)
Smokers	11.8%	0 (0.01)	4.6% (0.01)

*level of significance by nonpaired t-test of difference from Phoenix cohort
mean ±1 SD pressures in mmHg
lipid values in mg/dl

Although the Phoenix group data seems to parallel the results of general population studies, when we lok at each of the three variables individually, we get a different perspective. If we compare the cholesterol values for the Phoenix physicians with the 1983 AMA guidelines for hypercholesterolemia,[15] we find that the group has a consistently higher 90th percentile cut point than the Lipid Research Clinics' (LRC) norms for all age groups (Table 8), ranging from a low of 11.4% to a high of 19%. Furthermore, when compared with the newly-established guidelines from the NIH Consensus Development Conference for cholesterol levels to prevent heart disease,[11] anywhere from 18.2% to 28.6% of the Phoenix physicians could be assigned to the moderate risk group depending on the age-decade. From 9.1% to 14.3% of the physicians fell into the high risk category for the cholesterol risk factor. It would appear that the cholesterol profile for the Phoenix physicians as a group deviates considerably from ideal.

In terms of blood pressure, we were impressed with the level of systolic and diastolic values we encountered in the Phoenix group. The prevalence of elevated blood

pressures (>95 diastolic and/or >160 systolic) in these men (4.7%) was significantly lower than what we would expect to find in the general white male population; however, the number of participants with a history of hypertension (13%) raised the total hypertensive prevalence in this group to nearly 18%, just below the one in five rate of occurrence in the general population.

A great deal of information is available relative to cigarette smoking. Since the anti-smoking campaign began in the 1960's, there has been a gradual decline in the smoking rate in the United States.[16] However, among physicians, the drop has been impressive. Enstrom[4] surveyed California physicians and found a decrease in smoking from 53% in 1953 to 10% in 1979. Indeed, when we compare our physician data with recent national data on smoking from the Minnesota Heart Study, the National Center for Health Statistics,[17] and the Behavioral Risk Survey[18] (Table 9), we see just how much better than the general public the physicians as a group have heeded the smoking warnings.

Table 8
Comparison of 90th Percentiles Between LRC Males[15] and Phoenix Physician Males for Total Cholesterol (mg/dl)

Age	Physicians	LRC Males	%Exceeding LRC 90th %ile
30-39	259	234	17.0
40-49	266	254	12.9
50-59	276	261	19.0
60-69	269	258	13.1
70-79	258	249	11.4

Table 9
Comparison of Smoking Rates Between Phoenix Physicians and Various General Population Studies (Males Only)

Age Group	Phoenix Physicians (1983)	Minnesota[13] (1980-2)	NCHS[17] (1980)	Behavioral Surveys[18] (1981)
25-34	10.0%	40.5%	42.0%	36.0%
35-44	11.8%	36.1%	42.4%	42.4%
45-54	9.7%	35.6%	40.0%	40.2%
55-64	10.5%	25.4%		
all ages	10.3%	34.5%	37.1%	34.0%

However, among those smokers in the Phoenix study, the greater prevalence of elevated blood pressure and cholesterol levels (see Table 5) compounds the risk imposed by smoking, making their overall risk profile higher than their nonsmoking colleagues. In fact, based on the Framingham Risk Factor Probability Tables,[1] the physician-smokers have nearly twice the probability of developing coronary artery disease over a six year period (6.7 as compared to 3.6 for nonsmokers).

We all hope that with knowledge will come the wisdom and foresight to know how to apply what we have learned for our betterment. Certainly, when it comes to disease prevention, no group is better prepared to utilize the abundant, newly emerging principles of prevention than healthcare professionals. The data from the Phoenix Physicians' Risk Factor Evaluation would seem to substantiate the view that physicians smoke less than the general population and have about the same prevalence of high blood pressure, but the cholesterol level across all age strata are cause for concern. Moreover, physician-smokers have a higher prevalence of associated risk factors and therefore a significantly greater probability of developing heart disease. Hopefully, continued awareness and application of prevention techniques among physicians will lead to an improved profile in the years ahead.

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Community Health Action On Wheels: Primary Care As a Vehicle for Community Change

Abstract

This paper describes the unusual utilization of a mobile medical clinic in rural medically underserved communities in Arizona for the purpose of mobilizing community interest and resources around health care. The mobile unit previously served the population of five small communities, resulting in considerable community organization improvements and/or establishment of permanent health facilities. The Rural Health Office of the University of Arizona's College of Medicine implemented a demonstration study of this approach to record, observe and evaluate its effectiveness as a means of stimulating the development of community-oriented primary care services. The small Hispanic community of Continental, Arizona was selected; an informal needs assessment was conducted; and a series of community organizing activities were carried out. Subsequently, this community joined with two other small rural communities to form a permanent medical care consortium, sharing clinical, administrative and management services. A mobile unit can serve as the necessary catalyst to bring lasting responsive health care to rural communities.

Key Words: Arizona, Community-oriented Primary Care, Community Participation, Mobile Unit.

Introduction

Mobile health clinics have increasingly been used as a response to a scarcity of health services, resulting from the maldistribution of medical manpower. In rural areas they have been employed to serve specific population groups or to fulfill specific health needs.[1] Recently reported examples include a mobile unit providing internal medicine services to veterans in Colorado, a podiatric clinic for migrant farmworkers in California, a family planning clinic in Florida, and rehabilitation services for residents of a mountainous region of Colorado.[2-5] With the growing emphasis on health maintenance and disease prevention, mobile units have been used with increasing frequency to provide health education and screening for specific health problems.

The mobile medical clinic's concept to combine health maintenance functions with the delivery of primary health care services to underserved rural populations was developed by the Department of Family and Community Medicine of the University of Arizona's College of Medicine. The major intent of the clinical unit was to help communities to organize and develop their own permanent health care facilities. Once the target community became organized for health care, it could then use its organization to pursue other community improvements.

The methodology of combining community organization with the use of the mobile clinic was developed by one of the authors (AO) as an outgrowth of his experience with rural health care in Arizona. This paper discusses the historical development of the mobile clinic model and outlines its implementation in the context of promoting community organization to improve health care in a rural community in southern Arizona.

Background

Between 1975 and 1980, the Department of Family and Community Medicine of the University of Arizona operated a mobile clinical unit in five different rural communities in southern Arizona for the purpose of delivering primary care services in underserved communities and stimulating the interest of the residents in bringing about community improvements and planning for long-term health care needs. The role of the mobile clinic and the outcome of its involvement varied from one community to another according to the needs and demographic characteristics of the communities. Table 1 presents a summary of the experiences of the mobile unit in the five communities. In all cases, the mobile clinic served as more than a source of primary medical care; it was a focal point for community organization, and a source of assistance and encouragement to community members and leaders interested in improving their living conditions and developing permanent health care facilities.

In the Marana Yaqui Village and Rillito, very small communities with predominantly minority populations, the mobile clinic helped to bridge the cultural gap which had discouraged residents from using the existing Marana Clinic facility. In Tombstone and Catalina the mobile unit was a catalyst to improve support to existing community efforts to establish permanent health care facilities. In Maricopa, functioning as a satellite of the West Pinal Family Health Center, the mobile clinic tested the need and demand for primary health care services in the area, acquainted the community with the services of midlevel practitioners, and resulted in a permanent satellite facility.

The Model and its Implementation

The approach used by the mobile clinic to respond to specific needs and problems characteristic of many rural

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southwestern communities is summarized in Table 2. The actual steps involved in the implementation of the mobile clinic model from the selection of a site to the establishment of a health care facility are diagrammed in Figure 1. A brief narrative description of this four-phased approach follows as it applies to a specific community where the model was extensively analyzed and evaluated for demonstration purposes.

Site Selection (Phase 1)

A primary constraint in selecting the site for the mobile unit project was that it be within reasonable commuting distance of the city of Tucson for the purpose of personnel convenience. Along the highway corridor which links Tucson with the dual border towns of Nogales, Arizona, and Nogales, Sonora, Mexico are several small, predominantly Hispanic communities. From

Table 1
History of Mobile Clinic Unit in Five Rural Communities of Southern Arizona
1975 — 1980

	Community				
	Marana-Yaqui Village	**Rillito**	**Tombstone**	**Catalina**	**Maricopa**
Population	100	300	1500	3000	5000
Income Level	Low	Low	Low-Moderate	Low-Moderate	Low-Moderate
Ethnic Composition	Native[1] American	60% Black, 30% Hispanic	25% Hispanic	10% Hispanic	30% Hispanic, 15% Native American, 5% Black
Unemployment Status	High	High	High, retired community	Moderate	High/Farmworkers
Dates of Service	10/75—9/77		11/77—3/78	8—9/78	1/79—8/80
Funding Service	SOARHI[2]				Four Corners Regional Commission
	ARHF[3]		ARHF	ARHF	ARHF
Administrative Base	Marana Community Clinic		Benson Health Services	Catalina Community Health Services	West Pinal Family Health Center (Casa Grande)
Days per week	5 hrs/2 weeks		8 hrs/week	5 hrs/week	3 days/week
Staffing	U of A bilingual physician		Family nurse-practitioner, physician's assistant	Bilingual physician	Physician's assistant
Outcomes contributed to by mobile unit & community	Increased utilization of nearby clinic		Permanent clinic facility opened March, 1978	Permanent clinic facility opened July, 1981	Permanent clinic opened June, 1980
	Village improvements: sanitation, housing, streets, recreation	Community improvements: sewer system, park, community center, streets, day-care center			
Current medical staffing (full-time)	1 NHSC physician, 1 nurse practitioner		NHSC physician, physician's asst.	Nurse practitioner	NHSC physician, physician's assistant

1 Not covered by Indian Health Service until 1980
2 Southern Arizona Rural Health Initiative (1975-1976)
3 Arizona Rural Health Federation (1977)

these, the community of Continental, approximately thirty miles south of Tucson in Pima County, Arizona, was selected as the demonstration site. Reasons for its selection, in addition to its location and demographic characteristics, included the expressed interest of some community leaders in securing health services for the area. Of equal importance was the existence in the area of a framework of services which also impact on health status, such as a food bank, a well-baby clinic, social service counseling, employment programs, a housing development program and day-care.

Table 2
Mobile Clinic Approach to Meeting Community Needs

	Community Characteristics	Mobile Clinic Response
I.	Isolation	Travel to Community
	A. Geographic B. Cultural/ Linguistic	Bilingual physician and support personnel; experience in community programs
II.	Poverty	Sliding fee scale; encourage and facilitate enrollment in state indigent health care program; cooperate/communicate with agencies providing other forms assistance (energy, food, emergency, etc.)
III.	Inadequate Health Care Insufficient population and economic base to support full-time medical provider	Shared provider arrangements with other small communities. Provision of primary medical care with an emphasis on health promotion/disease prevention; assist community in organizing to establish a permanent health care facility. Establish linkages with with existing care resources. Utilize and teach value of mid-level providers.
IV.	Environmental Health Risks A. Inadequate Sanitary Facilities B. Inadequate Housing C. Unpaved Roads D. Exposure to Pesticides E. Hazardous Working Conditions	Heighten community awareness of relationship between environment and health status; encourage environmental improvement and help to identify sources of assistance. Encourage input into legislation concerning hazardous materials and working conditions.

Laying the Groundwork (Phase 2)

Formal surveys were nearly impossible to administer in the area surrounding Continental. Many households lacked telephones; and others lacked addresses. Therefore, in its needs assessment process the Rural Health Office relied heavily on key informants, including social services providers and knowledgeable community members, as well as on data compiled by the Pima County Planning and Zoning Department which had recently completed a study of the area.[6] All indicators confirmed the impression that Continental and the surrounding rural area contained an appropriate target population with a high unmet need for primary health care services.

The single most important step in preparing the community for the mobile clinic project was a community meeting held prior to the arrival of the mobile unit. At this meeting the medical director, who also served as the principal field physician, spoke in Spanish and in English, describing the philosophy of health care and stressing the importance of community participation. The audience was encouraged to make a list of the services they would consider necessary and desirable in a broad-based primary care program. Then a list of services already in place or accessible was made and matched against the desired list. The importance of community participation in bringing the missing, needed elements of service was emphasized. Afterwards, seven people volunteered to serve on a Clinic Advisory Committee. The first meeting was held at the community center where the mobile unit was parked. Opening day of the clinic was carefully selected to coincide with Mexican Independence Day, 1981.

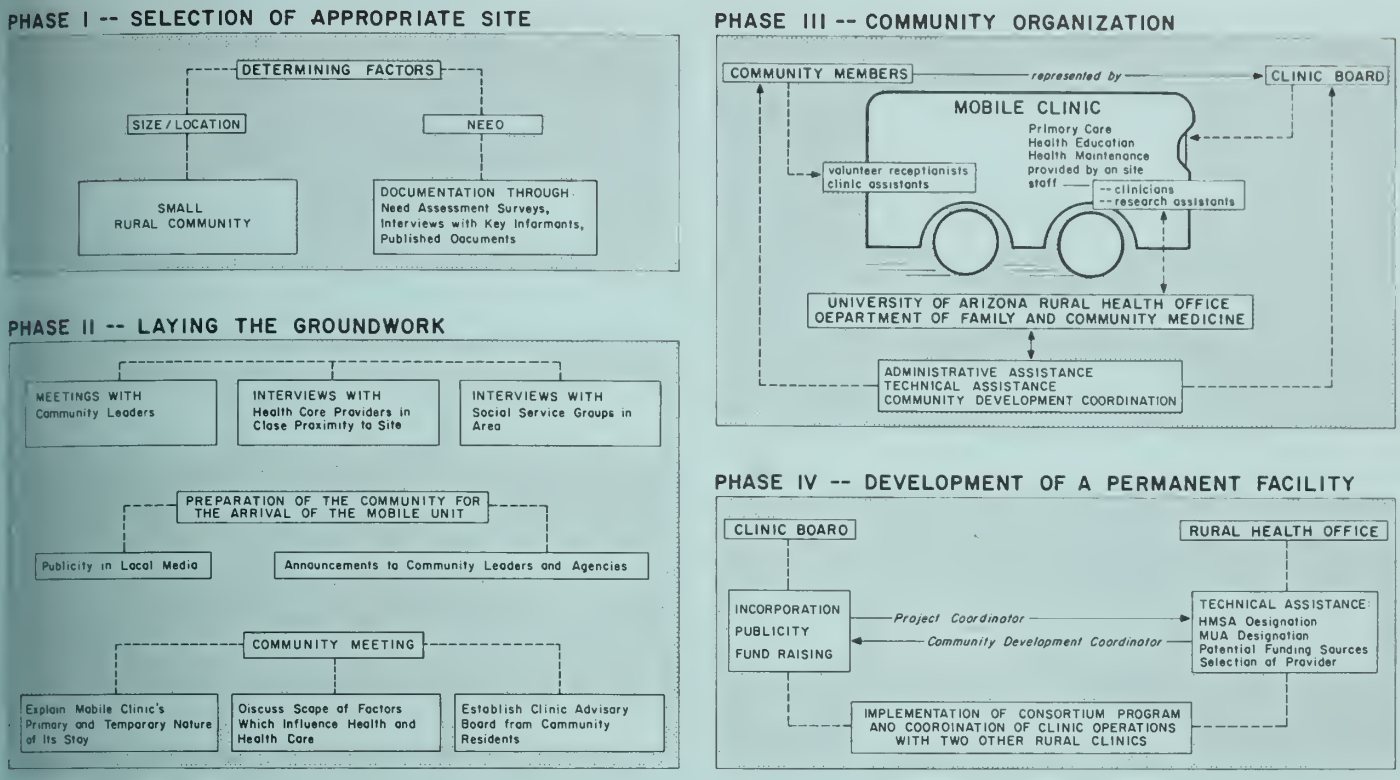
Community Organization and Development of a Permanent Clinic Facility (Phases 3 and 4)

The original Clinic Advisory Committee functioned well for six months, by which time clinic utilization had become substantial enough to enable the Committee to expand services and to begin incorporation of the clinic Board of Directors. It was this group which became responsible for policy decisions, fund raising events, and acquisition of funding for a permanent clinic building.

In its early stages of development the clinic board was unable to acquire the funds needed to provide salaries for permanent clinic personnel and to cover the clinic's other operating expenses. At this point, the assistance of the University of Arizona's Rural Health Office was crucial for the fledgling program's survival. With its knowledge of potential funding sources and experience in applying for government grants, the Rural Health Office staff helped the clinic identify possible sources of support and apply for start-up funding. The mobile unit functioned as the temporary clinic facility for a period of two years.

The low average income of the clinic's patient population required financial subsidy to make the clinic viable. This anticipated need was the basis for an agreement among the community of Continental and two other small communities in Pima County, in collaboration with the University of Arizona's Department of Family and Community Medicine, to merge administrative, management and medical service operations. In addition, these rural sites shared a health care provider supplied through the federal program of the National Health Service Corps.

In the Spring of 1983, as a result of this agreement, the three small rural part-time clinics in southern Pima County formed a consortium, the United Community


PHASE I -- SELECTION OF APPROPRIATE SITE
DETERMINING FACTORS
SIZE / LOCATION
NEED
SMALL RURAL COMMUNITY
DOCUMENTATION THROUGH Need Assessment Surveys, Interviews with Key Informants, Published Documents
PHASE II -- LAYING THE GROUNDWORK
MEETINGS WITH Community Leaders
INTERVIEWS WITH Health Care Providers in Close Proximity to Site
INTERVIEWS WITH Social Service Groups in Area
PREPARATION OF THE COMMUNITY FOR THE ARRIVAL OF THE MOBILE UNIT
Publicity in Local Media
Announcements to Community Leaders and Agencies
COMMUNITY MEETING
Explain Mobile Clinic's Primary and Temporary Nature of Its Stay
Discuss Scope of Factors Which Influence Health and Health Care
Establish Clinic Advisory Board from Community Residents
PHASE III -- COMMUNITY ORGANIZATION
COMMUNITY MEMBERS
represented by
CLINIC BOARD
MOBILE CLINIC
Primary Care
Health Education
Health Maintenance
provided by on site staff
volunteer receptionists
clinic assistants
--clinicians
--research assistants
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TECHNICAL ASSISTANCE
COMMUNITY DEVELOPMENT COORDINATION
PHASE IV -- DEVELOPMENT OF A PERMANENT FACILITY
CLINIC BOARD
RURAL HEALTH OFFICE
INCORPORATION
PUBLICITY
FUND RAISING
Project Coordinator
Community Development Coordinator
TECHNICAL ASSISTANCE
HMSA Designation
MUA Designation
Potential Funding Sources
Selection of Provider
IMPLEMENTATION OF CONSORTIUM PROGRAM AND COORDINATION OF CLINIC OPERATIONS WITH TWO OTHER RURAL CLINICS

FIGURE 1. IMPLEMENTATION OF THE MOBILE CLINIC MODEL

Health Center, Inc. (UCHC) which enabled the clinics to share services. A Governing Board was established, composed of an equal number of representatives selected by each of the local community committees, to determine all policies and procedures for the consortium program.

In March 1984, the UCHC, in collaboration with the Rural Health Office, received community health center funds from the Department of Health and Human Services. This federal award, to be transferred directly to UCHC in the spring of 1986, enabled the clinics to hire local clinic personnel, set up administrative and management procedures, purchase equipment and supplies, expand clinic schedules, and offer new health care services. Uniform billing and collection procedures, fee schedules, and medical records and quality assurance systems were developed. A desired outcome was that the merging together of small rural clinics would result in an increase in the productivity and quality of health care services and prove useful in the planning process for other rural community health centers. An exciting component was the observation of change in Continental community residents, who three years prior to consortium development were unsure of their participation in a community-based health program, and gradually became stimulated into forming an alliance and working as full partners with two other rural communities.

Discussion

The experiences of the mobile clinic project in Continental, as well as in the five other rural communities in southern Arizona, demonstrate that a mobile clinical unit can be an effective device to encourage community organization and participation in health care planning and clinic development.

The process of community organization used in this demonstration project is in many ways analogous to the clinical approach to the individual patient advocated by Kleinman, Eisenberg, and Good.[7] This approach involves eliciting the patient's model of his illness, communicating the doctor's model to the patient, and negotiating a mutually satisfactory, shared model which results in greater understanding and acceptance of treatment. As Kleinman has stated, "how we communicate about our health problems, the manner in which we present our symptoms, when and to whom we go for care, how long we remain in care, and how we evaluate that care are all affected by cultural beliefs."[8] Just as cultural beliefs shape the individual patient's view of illness and health care, cultural beliefs also shape the expectations of the community as to what constitutes appropriate or acceptable care. Oftentimes, there is a lack of understanding by health care providers functioning in the biomedical western style of health delivery of the native or folk healing art. However, this void can be filled if the health professionals are aware of and sensitive to the community's culture and its existing traditional medical systems.[9] It is, of course, critical for the community to have confidence in health professionals and their methods. Successful implementation of the mobile clinic model

clearly requires personnel with experience and/or training in human and community relations. The mobile clinic project had as its medical director an experienced physician who was not only bilingual but was also sensitive to cultural nuances, human needs and behavior. The success of the community organization efforts described in this paper was primarily due to experienced and skillful leadership. With mutual understanding of expectations and needs it was possible to enlist from the onset cooperation and enthusiasm on the part of the community and project staff.

It must be noted that the expectations of the community of Continental were focused more on the treatment of illness rather than on prevention and health promotion. Health education was most effectively provided during clinician-patient interactions. The screening clinic established for women (which included low cost pelvic examination, Pap smear, instruction in breast self-examination, hematocrit and urinalysis) was well attended by Green Valley residents but utilized minimally by the Hispanic population of the mobile clinic project. This finding corresponds to experiences reported by Wolinsky,[10] Kronenfeld,[11] and Becker[12] which indicate that lower income populations make less use of discretionary services and are more likely to respond to the need for medical services because of illness. The health belief model of Becker assumes that the greater the educational level, the more likely an individual is to engage in elective and preventive health behavior.[13] As pointed out by Wolinsky, the value structure of the group is a strong governing factor in patterns of utilization of care.[11] For people who are forced to live from day to day, oftentimes health care may be considered a luxury. Out of necessity, crises—such as acute illnesses—must be attended to first. Furthermore, consumer attitudes about health care are a reflection of the provider's philosophy and attitudes. Emphasis on prevention, health maintenance, and health education is a recent development, and its promulgation takes time. The community must have a focus on and participate in plans for health education and be given time to develop awareness of the need for and value of prevention programs. For the underserved rural residents of Continental, the mobile unit provided this focus.

The Rural Health Office recognizes that the use of a mobile medical unit is not a substitute for comprehensive health care but an introduction for rural residents to primary care services. Many planners in the past have found that mobile health care units have been used in a mobile service delivery mode. In southern Arizona, the approach has proven successful—not only in improving access to health services for six rural communities, but also in creating a sense of consumer ownership and participation within those communities. The documentation of this unique community action effort may provide a stimulus for the health care planners, policy-makers, medical providers, and community leaders to explore innovative approaches toward achieving the goal of quality health care for all people.

Acknowledgements:

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Neurologic Tissue Transplants — Are They Possible?

Transplantation has become an accepted form of medical therapy for end-stage disease of various organs following advances in biomedical ethics, surgical technology, tissue typing and immunosuppressive therapy. The general acceptance that brain death is synonymous with mortality allows the harvesting of viable organs from individuals without residual brain function, most frequently following massive craniocerebral trauma. However, the brain and the remainder of the central nervous system (CNS) comprise the penultimate human organ with twenty billion neurons providing the essence of human life, intellect, emotion, motor control, environmental awareness, processing and storing information as nature's most sophisticated supercomputer. What possibilities, therefore, exist for replacement of all or part of the CNS?

The human brain has unique anatomic and physiologic properties. The absence of lymphatics and the ultrastructural blood brain barrier reduces its immunogenicity, increasing the likelihood of successful neurologic tissue transplantation. However, the inability of neuronal tissue to regenerate readily and the complexity of CNS architecture will most likely limit complete organ transplantation to grafting or implantation. It has been established that most central neurons have the ability to grow, generate processes and develop new synaptic connections long after the embryonal stage. This property, collateral sprouting, occurs only in intact neurons in response to adjacent injury while damaged central neurons cannot regenerate. Furthermore, newly-formed synaptic connections are not necessarily anatomically or physiologically correct. Therefore, two vital elements are required for functional CNS replacement: 1) neurons with the capacity to extend processes must be present, and 2) the regenerating cells must find a continuous, unbroken pathway to targets capable of reinnervation through a supportive milieu.

The ability of neurologic tissue to survive and grow after transplantation into the CNS or elsewhere has been known for a long time. Ramon y Cajal in the 1890's implanted pieces of peripheral nerve and dorsal root ganglia into the brain in an attempt to transfer the regenerative capacities of these tissues. A few years later, Thompson successfully transplanted pieces of mature cat cerebral cortex into the cerebral cortex of adult dogs which remained viable histologically for months thereafter. White, et al., maintained viability of 63 monkey brains with sophisticated extracorporeal systems and transplanted a whole dog brain preparation into the neck of a recipient dog, with electrocortical activity persisting for days. Deminkov, in the late 1960's, transplanted entire dog heads with asculature to the necks of recipient dogs, with 19 of these second heads surviving up to 29 days.

"The transplanted head reacted briskly to the surroundings, had an intelligent expression, licked when it saw a bowl of milk and eagerly lapped up milk or water. When the recipient dog stood up and the transplanted head experienced discomfort or pain, it bit the recipient dog behind the ear. The transplanted head fell asleep irrespective of whether the recipient dog was asleep or awake."

The current state of CNS tissue transplantation is, however, far removed from complete functional organ replacement. It is known, largely through the work of neurobiologists working with small rodents, that transplanted neurons can survive in the host brain, establishing function of sorts by developing processes and synaptic connections. Some transplanted neurons can organize into anatomic configurations similar to the portion of brain from which they originated with functional synapses that secrete neurotransmitters and generate action potentials. Based on this information, neurologic tissue transplantation is primarily following two basic approaches, which include neuronal and tissue transplants and peripheral nerve-axonal bridge implants.

Embryonic donor neurons have been successfully transplanted into the neuraxis of both immature and adult hosts. Transplants remain viable, differentiate and interact anatomically and physiologically with the host tissue. For example, Sunde and Zumner of Denmark have transplanted rat embryonic hippocampal region tissue into various areas of immature rat brain. The transplants developed the normal histologic appearance of hippocampus independent of the recipient area of brain. Even though these grafts were viable they remained nonfunctional. If transplanted to the hippocampal region, however, apparently functional cholinergic afferents innervated the implanted tissue. Thus far, functional transplants of rat locus ceruleus, hippocampus, septal tissue and pituitary have been accomplished. Rats with septal transplants into the region of fornix-fimbria lesions which produce impairment in maze learning, demonstrated dramatic improvement in ability. These results provide the first indication that neurologic tissue transplants can improve lesion-induced deficits in behavior. Transplantation of embryonic substantia nigra to the lesioned nigrostriatal pathway of adult rats rendered improved motor dysfunction in animals with Parkinson-like disorders.

Aguayo has utilized peripheral nerve grafts as a structural template or bridge to allow growth of processes from neurons in lesioned areas at all levels of the CNS. The peripheral nerve transplant, in a manner as yet unknown, stimulates either the injured neurons or intact nearby neurons to regenerate and sprout processes growing in the peripheral nerve conduit similar to regenerating peripheral nerve fibers, allowing for the stimulation and direction of growth of central neurons. The regenerating fibers, however, have yet to be demonstrated to make functional connections with recipient tissues. However, several neurotrophic factors (substances promoting growth or survival) in areas of neural damage have been identified.

The future of CNS transplantation lies in developing the ability to transplant neural tissue to improve CNS deficiencies secondary to trauma, ischemia, neoplasm, degenerative or developmental abnormalities. The clinical potential for the use of peripheral nerve transplants to stimulate CNS fiber growth establishing pathways across bridges connecting damaged or defective brain or spinal cord

tissue, is readily apparent. Transplantation of specific types of neuronal tissue may replace that damaged or absent secondary to degenerative or traumatic processes. Isolation and identification of neurotrophic factors may improve survival and play a key role in the regrowth of absent pathways to deafferented areas. Currently, transplantation of adrenal chromaffin cells into the striatum in humans for the alleviation of Parkinson's disease is in progress. Since it has been proven experimentally that CNS tissue transplantation is capable of restoring innervation to nonfunctional neuronal pathways, future developments remain unlimited. The likelihood of complete, functional brain or spinal cord transplantation, however, remains remote because of the enormous anatomical complexity of the requisite CNS connections. Although the tantalizing possibility of maintaining a viable functional brain from a donor individual with failing support systems in a recipient healthy body with irreversible brain damage potentially exists, the question would certainly arise as to which individual would be the donor and which the recipient.

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Patient Recall Systems

Most physicians are interested in having patients come back for their periodic re-evaluations. A recent HEW study of private practices indicated that 59 percent of all patient visits result in a scheduled follow-up. In many cases these are annual reappointments; and in some cases they are semi-annual; in more urgent cases they are in frequencies that are monthly or quarterly.

One of the casual ways of dealing with patients regarding annual visits is to suggest that they call or come in on their birthday. Some people forget (after all, who wants to think about a doctor's appointment in conjunction with a birthday celebration?) Another problem is that many people may wish to come in on their birthday month, and that may be the month when the doctor may want to take two, three or even four weeks of vacation. Therefore, we get a too-heavy load of these visits just before and just after the doctor takes his vacation.

Asking patients to call in 3 months or 6 months for that type of appointment also doesn't work well. Many patients forget. Other patients are anxious, and they call in advance of when they are supposed to come in.

There is another problem with scheduling patients far in advance. We've already indicated it is very easy for some patients to forget, even if you have given them a firm appointment. The other problem is: they may, on short notice, call and reschedule due to some other, more pressing business. When they call to reschedule the appointment, they generally do not want to wait a significant period of time and may be taking away appointment slots that should be saved for more urgent patient visits.

Another weakness in setting specific appointments far in advance is that the patient, for another or allied medical problem, may be in before the appointed date and the need for the previously established appointment time may be eliminated. Therefore, we have the potential of "no-shows" for such patients.

A further disadvantage of making appointments 3, 6 and 12 months in advance is that it "locks" the doctor in. If you want to take a day off, or a few days off, you wil have to call patients that are scheduled for those dates and reschedule them. This is not only costly, but can result in bad patient public relations.

Finally, some practices resort to telephoning patients as a reminder technique. This means that we have to have these names recorded in some sort of log which is quite expensive to maintain. When we telephone, what if the phone company tells us the phone is no longer in service? Does that mean the patient has moved? Is the phone disconnected? What if the patient doesn't have a phone? What if the patient is not at home from the hours of 9:00 a.m. to 8:00 p.m.?

The above systems just don't work too well. I'd like to recommend a better approach. A better approach involves not just one idea, but a few sequential ones which I'll explain in five simple steps.

Step #1 — Doctor Communications

You should have a well-designed charge ticket which makes it easy for you to note when you would like this patient to be seen again. This non-verbal communications tool helps your front office ladies estimate when the patient should be seen again.

Step #2 — Reminder Mailing

The patient does your clerical work, by addressing an envelope to him/herself. The envelope contains a reminder card which is already inserted. The reminder card says: "Please call the office for your examination. The doctor thinks this is important for your continued well-being."

Step #3 — Coding the Recall Visit

At the top right corner of the envelope, where you will eventually place a postage stamp, you will put a code indicating when the patient is to come back and when the patient was last seen. For example, 6/12 means the patient is to be back in June and was last seen in December; 6/6 means the patient is to be seen in June and was last seen in June; 6/3 means the patient is to be seen in June and was last seen in March. Obviously, the higher priority, for recall purposes, would be given to the patient who's coming in after 3 months.

All envelopes with a 6 on the numerator are placed in a June storage box, to be mailed in May. (Shoeboxes are very handy for storing these envelopes.) Starting in early May we could send out reminder mailings to those patients who have the higher priority, i.e., 6/3, 6/4 as compared to 6/6 and 6/9. A postage stamp is placed over the code numbers.

Patient appointment reminder cards are not all sent out in one big batch. We send out a few each day so we are not deluged with phone calls.

Step #4 — Patient Data Maintained

Every envelope going out of your office should have the following 3 word message below your return address — **"Address Correction Requested."** Envelopes having this message instruct the post office to provide you with a new mailing address (for a fee of 25 cents) should the patient have moved. It would help you have that intelligence. You may wish to send a letter to this patient suggesting that he/she seek a new physician in the new community for health maintenance purposes.

Step #5 — Dealing With High Priority or High Risk Patients

If seeing a patient is very important and you are concerned about the possibility of mailing out a reminder card and not hearing from the patient, there is something you may wish to do. The simplest thing you could do is to buy colored, self-adhering dots, 1/2" to 1" in size, that

could be affixed to the edge of the patient's file folder. A small, green dot could be used for the month of June, for example. When that June patient comes in, the receptionist peels the dot off the chart. At the end of the month of June, if we see any charts that still have small, green dots affixed, we would pull them and call the patients to get them in, or send them a second reminder note.

The other alternative is to maintain a hand-written monthly log for high priority patients and try to reach them: first by phone; if we can't reach the patient by phone, we'd try to send a mail reminder.

I recommend the 5-step approach above. Obviously, you can adapt these with variations that may work better for your practice.

Co-authors George C. Conomikes and Richard E. Kirkpatrick of Conomikes Associates, Inc., a medical practice management consulting firm headquartered in Marina del Rey, California. Mr. Kirkpatrick runs the Arizona office in Chandler, Arizona.

Briefly Noted

Robert S. Eliot, M.D., Phoenix, was honored as the first recipient of the John P. McGovern Medal or preeminance in medical communication at a luncheon ceremony in Montreal, Canada, on October 31, 1985. Dr. Eliot, author of "Is it Worth Dying For?," was cited for "his outstanding accomplishments in integrating concepts from psychology, physiology, and cardiology into an innovative program and then communicating this break-through to both the scientific and lay communities." The 2600-member American Medical Writers Association is a non-profit professional society devoted to the improvement of communications in medicine and allied fields.

Christian F. Risser V., M.D., Phoenix, recently made medical history in Payson when he performed the first cataract surgery in Payson. Dr. Risser, who practices in Phoenix, has maintained an office in Payson for more than five years. His grandfather became Payson's first medical doctor when he established his practice there in 1912.

Lowell G. Yardon, M.D., Phoenix, was recently appointed to the Board of Trustees of Humana Hospital, Phoenix. He is a former Chief of the Medical Staff of the hospital.

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In Memoriam

Dermont Wilson Melick, M.D., 75, a leader in establishing a medical school in Arizona and member of a pioneer medical family, died July 20, 1985, at Good Samaritan Hospital.

Dr. Melick successfully led efforts to locate the medical school at the University of Arizona in Tucson, despite the opposition from Phoenix colleagues who wanted the school at Arizona State University. The school opened in 1963 with Merlin K. DuVal, M.D., as dean.

Dr. Melick, an outspoken foe of what he called "medical stuffiness," often was in the forefront of issues that embroiled the state's medical profession.

One of those issues was his unsuccessful fight against a state law mandating continuing medical education for doctors.

He was born in Williams on March 3, 1910, the youngest son of Prince Albert Melick, M.D., and Cora (Wilson) Melick.

Dr. Melick graduated from the University of Arizona in 1931 and from the University of Pennsylvania School of Medicine in 1935. He returned to Williams and entered general practice with his father, who made house calls on a motorcycle.

After the elder Melick died in 1935, his son practiced in Williams for four years. He then left to take postgraduate medical and surgical courses at the universities of Michigan and Wisconsin, earning a master's degree and a doctorate in science, respectively.

Dr. Melick, now a certified chest surgeon, came to Phoenix in 1945 to practice his specialty. His colleagues considered him one of the best in the field.

Dr. Melick was president of the Maricopa County Medical Society in 1951 and the Arizona Medical Association in 1959. He also was a longtime commissioner and Arizona chairman of the Western Interstate Compact for Higher Education, the director of the Arizona Regional Medical Program serving rural areas, and a professor of surgery at the U of A College of Medicine.

Although a specialist, Dr. Melick extolled the general practice of medicine.

"The true priesthood of the medical practitioner is vested solely in the family doctor and his practice of general medicine," Dr. Melick wrote in his privately published autobiography, *Thunderbolt.* "All others are pretenders to the throne who fail to pay proper respect to those (doctors) doing the basic, important work of taking care of the individual sick viewed as a whole person. There is no substitute for general-practice experience."

Dr. Melick was the author of more than 35 scientific articles and the recipient of numerous honors and awards from local and national medical organizations.

He was the author of a letter to the editor published recently in *The Phoenix Gazette* in which he argued against banning smoking in public places. He wrote an article on the same subject that appeared in the June issue of *Private Practice*, a medical publication.

Among awards Dr. Melick received were the Merit Medallion (1960) and the Distinguished Citizen Award (1966), both from the University of Arizona; and the Joseph Bank Medal of the Maricopa County Medical Society (1967).

The Phoenix Historical Society in 1977 named Dr. Melick and his father Arizona medical pioneers.

Survivors include his wife Dorothy Helen; two sons, Richard and John, and a grandchild.

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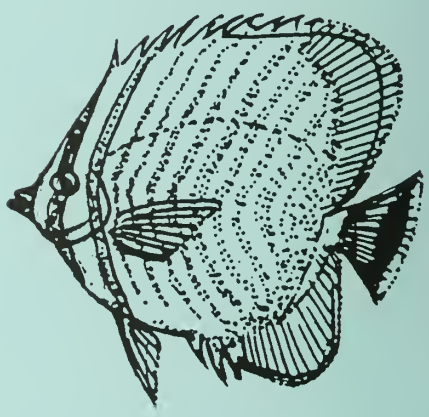

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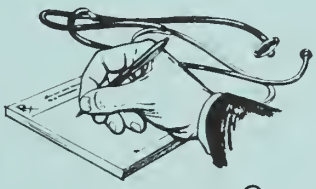

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Clinical Investigation

Pulmonary Alveolar Type II Epithelial Cells and Adult Respiratory Distress Syndrome

ROBERT J. MASON, MD, *Denver*

During the past ten years, functions of alveolar type II cells have been well characterized with isolated cells in vitro. Some of the functions were well known from studies in vivo, but others such as transepithelial sodium transport were unsuspected. A better understanding of this important pulmonary cell type improves our knowledge of the pathophysiology of adult respiratory distress syndrome and may in time lead to new therapeutic strategies.

(Mason RJ: Pulmonary alveolar type II epithelial cells and adult respiratory distress syndrome [Clinical Investigation]. West J Med 1985 Nov; 143:611-615)

Over the past 25 years the emphasis of pulmonary research has shifted from gas-exchange physiology to pulmonary cell biology.[1] The assumption is that the development of rational pharmacologic treatment of pulmonary diseases requires knowing the cellular biochemical processes that underlie pathologic and normal pulmonary physiology. Because no single pulmonary cell type dominates in terms of mass or cell number,[2] biochemical studies of whole lung have been of limited value. Therefore, investigators have focused on the biochemistry of specific lung cell types. Recently progress has been made in the isolation and culture of alveolar and large airway epithelial cells, endothelial cells and mesenchymal cells. In this review I will focus on alveolar type II epithelial cells and the adult respiratory distress syndrome. The purpose of this brief review is to indicate how recent knowledge of cell functions of a specific cell type can suggest new pharmacologic approaches to an important pulmonary disease.

Alveolar Type II Cells

The alveolar epithelium is composed of squamous type I cells (membranous pneumocytes) and cuboidal type II cells (granular pneumocytes). An electron micrograph of a small portion of the alveolar epithelium is shown in Figure 1. Gas exchange takes place across the alveolar type I cell, the endothelial cell and their fused basement membrane. Type II cells contain characteristic lamellar inclusion bodies, the intracellular storage form of pulmonary surface-active material. Type II cells constitute 15% of total parenchymal lung cells and cover about 7% of the total alveolar surface area.[2] The main functions of type II cells are the synthesis, storage and secretion of pulmonary surfactant, maintaining the alveolar epithelium by serving as a stem cell for both type I and type II cells and transepithelial ion transport. Functions of type II cells have been reviewed previously.[3-5]

Adult Respiratory Distress Syndrome

The adult respiratory distress syndrome was originally described by Ashbaugh, Petty and colleagues in 1967.[6] The disease begins after some catastrophic insult—that is, multiple trauma, sepsis, aspiration or pancreatitis. After a quiescent period of 12 to 48 hours, diffuse pulmonary infiltrates develop, associated with a reduced compliance and progressive arterial hypoxemia. The clinical and pathologic features of the adult respiratory distress syndrome have been reviewed in detail.[6,7] In spite of significant improvements in respiratory care, the use of positive end-expiratory pressure, a new generation of antibiotics and nutritional support, the overall mortality remains about 60%.[8]

The adult respiratory distress syndrome has two temporal, sequential phases. The acute phase is characterized by widespread atelectasis and protein-rich pulmonary edema. This first phase is customarily managed by ventilatory support, a judicious use of diuretics and treatment of the underlying

EDITOR'S NOTE: Periodically, the Clinical Investigation Section of *WJM* will publish invited papers reviewing research areas that are of interest to its readers.

From the Lord and Taylor Laboratory of Lung Biochemistry, Anna Perahia Adatto Clinical Research Center and the Department of Medicine, National Jewish Center for Immunology and Respiratory Medicine, Denver.

This investigation was supported by grant Nos. HL-29891, HL-27353 and HL-33139 from the National Institutes of Health and a grant from Great West Life Assurance Company.

Presented at the Western Association of Physicians meeting, Carmel, California, February 6, 1985.

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Reprint requests to Robert J. Mason, MD, Department of Medicine, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St, Denver, CO 80206.

insult. The major abnormality is reduced compliance, which is thought to be due to a physiologic deficiency or "inactivation" of surface-active material. Pathologically, the lung shows diffuse alveolar damage to both the alveolar epithelium and the endothelium. Although some may state that damage to the epithelium or the endothelium is selectively more severe, the diffuse injury affects both cell types and both are involved in the pathogenesis of the disease.[7] The subacute phase is more variable and is characterized either by gradual improvement or by multiorgan failure, rapid pulmonary fibrosis and a stormy clinical course. During the second phase there is proliferation of type II cells and, in the survivors, gradual clearance of protein-rich pulmonary edema.[9] In spite of severe pulmonary insufficiency during the initial phase of their illness, most long-term survivors recover with only minimal residual pulmonary impairment.[10]

Synthesis, Intracellular Transport and Secretion of Pulmonary Surfactant

Synthesis, secretion and extracellular processing of surface-active material are very complex and are schematically represented in Figure 2.[11-14] Purified surface-active material is composed of saturated phosphatidylcholine (36%), unsaturated phosphatidylcholine (32%), phosphatidylglycerol (10%), specific apoproteins (5%) and other lipids.[11] In all mammalian species studied to date, the major group of surfactant apoproteins is a family of glycoproteins that has a minimal molecular weight of 32 to 38 kilodaltons as determined by polyacrylamide electrophoresis under reduced conditions.[15] These are the major surfactant apoproteins that accumulate in alveolar proteinosis. There is also a group of very hydrophobic smaller molecular weight proteins (11 kilodaltons) that has not been characterized as completely as the 32 to 38 kilodalton family.[15-17] As will be discussed below, the composition of surface-active material in vivo will vary at different phases of the cycle of surfactant processing (Figure 2). Phosphatidylcholine is synthesized on the endoplasmic reticulum. It remains uncertain what fraction of the phosphatidylglycerol used in surfactant is synthesized in the endoplasmic reticulum and what fraction is synthesized in mitochondria.[18] The structures where lamellae first appear are the multivesicular bodies. These structures accumulate more phospholipids and develop into lamellar bodies. Because lamellar bodies contain a variety of acid hydrolases, they are thought to be modified or specialized lysosomes. The perplexing biologic question of how the phospholipids designed for secretion as surfactant are sorted and segregated from phospholipids designed for cellular membranes remains unanswered. Surfactant is enriched in saturated phosphatidylcholine and phosphatidylglycerol and relatively deficient in sphingomyelin, phosphatidylethanolamine and phosphatidylserine, which are common phospholipids of most biologic membranes. Although we know a lot about intracellular trafficking and sorting of proteins, we know very little about the intracellular trafficking and sorting of phospholipids. Secretion occurs by classic exocytosis. Secretion in vitro is stimulated by factors that stimulate protein kinase A (derivatives of adenosine 3′:5′-cyclic phosphate [cyclic AMP], β-adrenergic agonists, cholera toxin and so forth) and protein kinase C (tetradecanoyl phorbol acetate, and 1-oleoyl-2-acetyl glycerol) and that alter intracellular calcium (A23187).[19] The major trigger for secretion in vivo is hyperventilation but the biochemical signal for this physiologic stimulus is not known.[20]

Extracellularly secreted surfactant forms tubular myelin, which is a unique physical form of a phospholipid bilayer; when it is cut in cross section it has right-angled corners,[21] as contrasted with the rounded concentric lamellae of liposomes. The formation of tubular myelin requires the lipids of surface-active material, the apoproteins and calcium.[22] Tubular myelin is formed in the fetal lung and in culture, which implies that neither an air-liquid interface nor breathing movements are required for its formation. Tubular myelin can also be formed or destroyed in vitro by adding or chelating

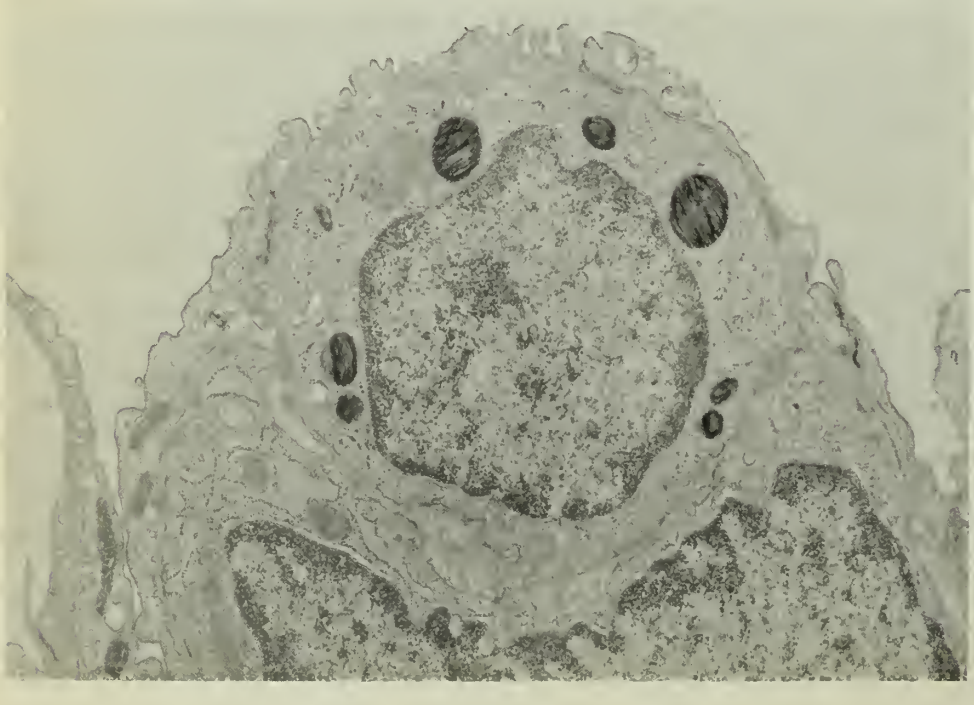

Figure 1.—Transmission electron micrograph of an alveolar type II cell. The type II cell is identified by the lamellar inclusion bodies that are the intracellular storage form of surface-active material. At the apex of the type II cell are characteristic microvilli. Above the type II cell is the alveolar space. Type I cells join type II cells at the apex of the type II cell and form tight junctions with the type II cell. Over to the left is a distended capillary that has been cleared of blood by perfusion fixation. Gas exchange takes place across the type I cell, the fused basement membrane and the endothelial cell. (Magnification, approximately 5,000 ×. This micrograph was provided by Mary C. Williams, PhD, University of California, San Francisco.)

calcium from purified surfactant.[22] The function of tubular myelin apparently is to facilitate the adsorption of surfactant to the air-liquid interface. Once adsorbed to the air-liquid interface, the composition of the surface monolayer is changed as the film is compressed during expiration. The unsaturated phospholipids and the apoproteins are squeezed out of the monolayer by the high film pressure as low surface tension is achieved.[23] The compressed surface monolayer is composed predominantly of saturated phosphatidylcholine and cholesterol, and the unsaturated phospholipids and apoproteins are displaced back into the alveolar fluid. Hence, during the normal processing of surfactant there is a physical separation of its components. The next step is controversial. As indicated in Figure 2, many investigators think that surfactant is taken up by type II cells and reutilized. However, the data to date are incomplete.[17,24-26]

Surfactant in Cases of Adult Respiratory Distress Syndrome

The first phase of the adult respiratory distress syndrome is physiologically a surfactant-deficiency state either due to inhibited adsorption of surfactant to the air-liquid interface by serum proteins,[27-29] cell debris or glycolipids[30] or due to decreased production or secretion. In the original description of the syndrome, Ashbaugh and co-workers pointed out the probable role of an alteration in surface-active material in the reduced compliance.[6] The reduced compliance can be due to altered surface forces, a decreased effective radius of curvature of the alveolar surface[31] or decreased tissue compliance. During the initial phase in animal models of the adult respiratory distress syndrome, the saline pressure-volume characteristics are not altered and therefore the tissue compliance is not significantly changed.[32] As will be discussed below, however, isolated surface-active material is abnormal and the effective radius of curvature for the Laplace relationship could be reduced due to the alveolar edema and hemorrhage.[31] The role of surface-active material in the pathogenesis of the adult respiratory distress syndrome has been reviewed recently.[33,34]

In cases of this disorder, there are reports of altered physical properties of surfactant,[35-37] and in animal models of the adult respiratory distress syndrome, compliance and gas exchange can be restored with exogenous surfactant.[38,39] The most interesting abnormality, however, is the altered composition of surfactant obtained by lavage in patients with the adult respiratory distress syndrome and in at least one animal model.[35,40] The change in the composition of isolated surface-active material implies some specific biochemical abnormality in type II cells. The physical alterations in surface-active material can probably all be accounted for by interference by the protein-rich exudate. Halmann and co-workers reported that the percentage of phosphatidylglycerol is specifically reduced.[35] In the fetus the synthesis of saturated phosphatidylcholine, phosphatidylglycerol and the apoproteins appears to be independently regulated.[12] One might speculate that after lung injury in adults, the repair process may simulate ontogeny. The implication is that factors that stimulate surfactant production in the fetus (glucocorticoids and fibroblast pneumocyte factor)[41] may also play an important role during the second phase of adult respiratory distress syndrome.

Pharmacologic stimulation of surfactant production in this disorder has not received much attention. To date, hormonal stimulation of surfactant production in adult type II cells in culture has been modest.[42] Ambroxol, a drug originally developed as a mucolytic agent, has been reported to increase production of surface-active material in adult animals and to prevent some forms of lung injury in animals.[43,44] However, the biochemical basis for these observed effects with ambroxol is not defined. Secretion of surfactant can be stimulated by β-adrenergic components but the most potent stimulant as judged by the in vitro data is protein kinase C. Agonists that activate protein kinase C in type II cells and that would be suitable for use in humans have not been reported, however.

Proliferation of Type II Cells

After the type I cells are destroyed in the course of the adult respiratory distress syndrome, the restoration of the alveolar epithelium is dependent on the proliferation of type II

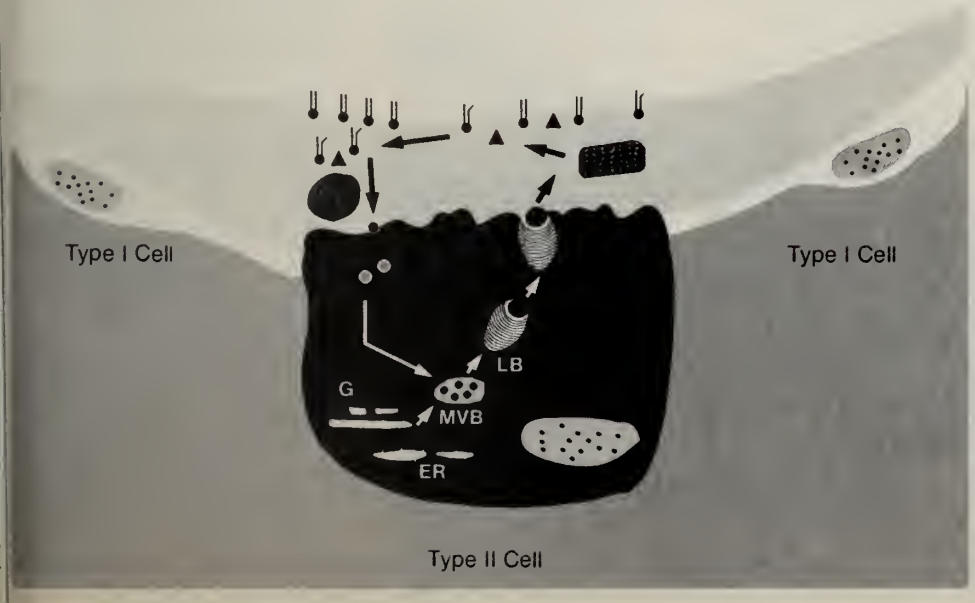

Figure 2.—Metabolism of surface-active material. This is based on current knowledge and will certainly be modified as new knowledge is acquired. ER = endoplasmic reticulum, G = Golgi body, LB = lamellar body, MVB = multivesicular body

cells (Figure 3). Type II cell hyperplasia is commonly seen several days after the clinical disease begins.[9] Haschek and Witschi proposed that the restoration of gas-exchange units after severe diffuse lung injury is dependent on type II cell proliferation.[45] Inhibition of type II cell proliferation prevents the restoration of the alveolar epithelium and leads to pulmonary fibrosis.[45] The control of type II cell proliferation in vivo is not known. In vitro a variety of factors stimulate DNA synthesis in adult type II cells in primary culture, and these include epidermal growth factor, insulin, cholera toxin, pituitary extract, hypothalamic extract (endothelial cell growth supplement), corneal endothelial cell extracellular matrix and media conditioned by macrophages.[46,47] Because macrophages accumulate at the time of type II cell hyperplasia in the subacute phase after lung injury, it is possible that the factor(s) made by macrophages is physiologically important. The major current problem with studies of proliferation of type II cells in vitro is that the cells appear to undergo only a single round of DNA synthesis so that although 50% of the cells incorporate tritiated thymidine as determined by nuclear labeling with autoradiography, sustained proliferation of adult differentiated type II cells has not been achieved. Likewise, to date we know of no factors that stimulate type II cells to proliferate in vivo. After destruction of type I cells in patients with diffuse lung injury, the first step in repair is to stimulate type II cells to proliferate to restore the alveolar epithelium. If we could pharmacologically initiate type II cell proliferation to repair the damaged alveolar epithelium, this might have a significant impact on the mortality of the adult respiratory distress syndrome.

Transepithelial Ion Transport

The alveolus is normally nearly free of fluid. Obviously, gas exchange is maximized by minimizing the amount of alveolar fluid. Conversely, gas exchange is significantly impaired by alveolar flooding, as occurs in cases of severe pulmonary edema. Although physiologists used to believe that the alveolar fluid homeostasis was regulated simply by passive forces, it is now clear that in the fetus during labor and in the adult, there is actual transepithelial transport of sodium

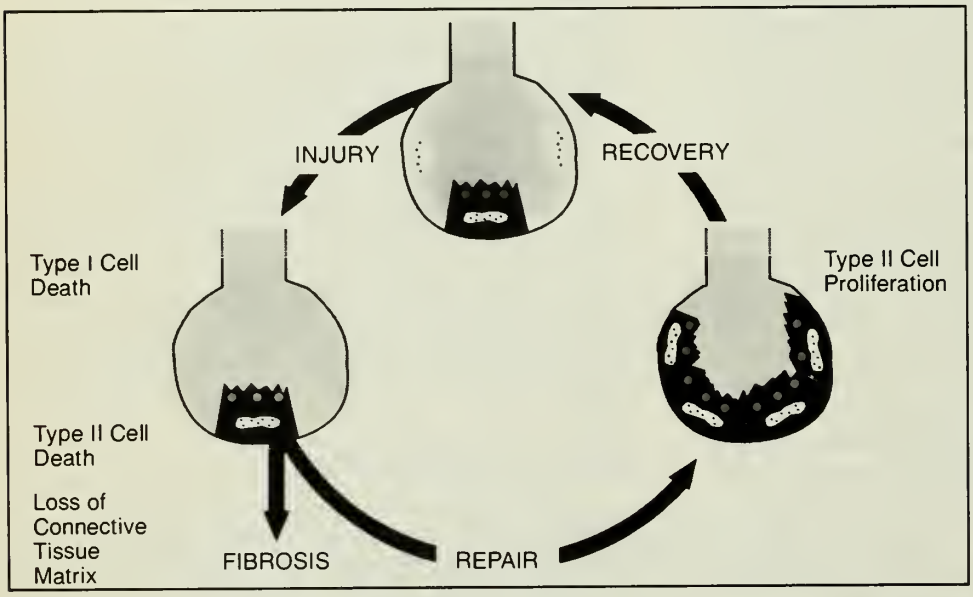

Figure 3.—A cartoon of lung injury and repair.

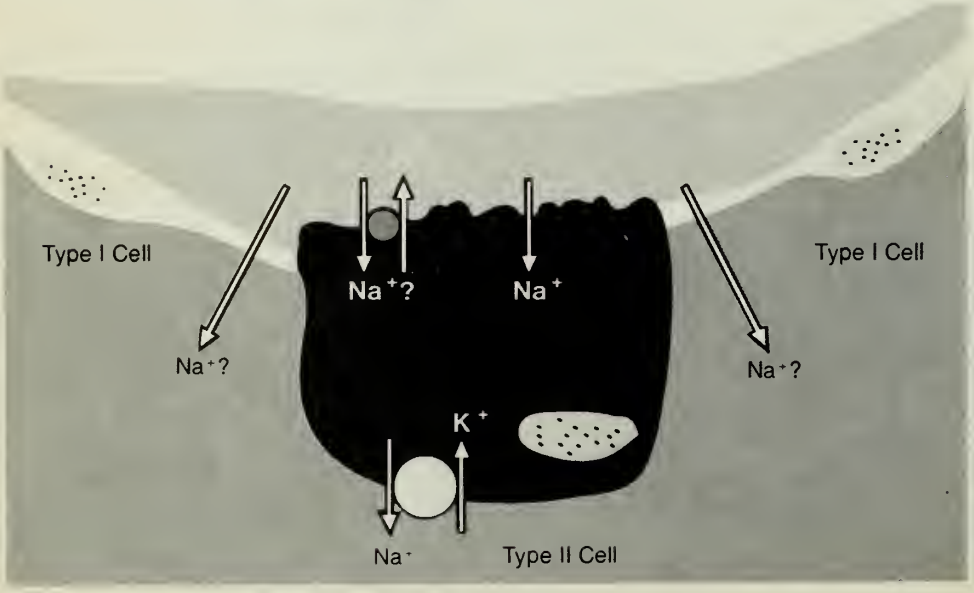

Figure 4.—Transepithelial electrolyte transport.

from alveolar fluid into the interstitium so as to keep the alveolus relatively dry.[48,49] As shown in Figure 4, in vitro type II cells transport sodium from their apical surface to their basolateral surface and net transport is stimulated by agonists that increase intracellular concentration of cyclic AMP.[50-53] Isolated type II cells form a pharmacologically and morphologically polarized epithelium in culture and ion transport is inhibited preferentially by amiloride on the apical side and by ouabain on the basolateral side. Ion current is completely inhibited by substituting choline for sodium in the bathing medium. Although the magnitude of this active transport process in the adult lung is not known, it is presumably important during the resolution of pulmonary edema, especially when the oncotic pressure of the alveolar fluid is high, as in patients with the adult respiratory distress syndrome. This is also a time when pathologically the alveolar epithelium comprises primarily hyperplastic type II cells.[9] Type II cells could be considered as little sump pumps in the corners of the alveoli. We do not know whether or not type I cells are involved in transepithelial ion transport, and that is the reason for the question marks in Figure 4. Similarly, we do not know if type II cells or type I cells are involved in the acidification of alveolar fluid[54] that could occur by a sodium-proton exchange process.

In summary, I believe the key to the development of new treatment modalities for the adult respiratory distress syndrome resides in better understanding of the physiologic functions of type I and type II alveolar epithelial cells. It is interesting to note that surfactant secretion, proliferation and transepithelial sodium transport are all stimulated by cholera toxin, which activates adenylate cyclase. Perhaps in the future, analogs of drugs that stimulate adenylate cyclase (such as cholera toxin or forskolin) will be used to treat patients with this disorder and reduce the mortality that has remained at about 60% for the past 20 years.

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Cimetidine Therapy for Gastroesophageal Reflux Disease

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In a Canadian multicenter trial, a new dosing regimen of cimetidine (Tagamet)—600 mg given twice a day—was compared with the standard regimen of 300 mg four times a day in 118 evaluable patients with endoscopically proved esophagitis. More than 90% of the patients evaluated had clinically moderate to severe esophagitis. After four weeks of therapy, both regimens had significantly reduced the number of episodes and the severity and duration of the worst episodes of daytime and nighttime heartburn, as evaluated by visual analogue scales. After eight weeks of therapy, this improvement persisted. There was no difference between the regimens. Healing was observed endoscopically in 57% of patients receiving cimetidine 300 mg four times a day and in 55% of those receiving 600 mg twice a day. Side effects were infrequent and minor.

(Archambault AP, Farley A, Cleator IG, et al: Cimetidine therapy for gastroesophageal reflux disease [Clinical Investigation]. West J Med 1985 Nov; 143:616-621)

The symptomatic treatment of gastroesophageal reflux disease consists of dietary and posture manipulations, weight reduction and avoiding excess alcohol, caffeine-containing beverages and tobacco products. Therapeutic agents include antacids, metoclopramide hydrochloride and H_2-receptor antagonists. Cimetidine is widely used in the treatment of this disease. In treating patients in North America who have acid-pepsin disease, cimetidine (Tagamet) is usually used in a dosage regimen of 300 mg taken four times a day with meals and at bedtime. In treating patients with duodenal ulcer disease, however, it has recently been shown that cimetidine, 600 mg given twice a day, is more effective than 300 mg taken four times a day in relieving nighttime pain and of equal efficacy in the healing of ulcers (P. Pare, A. Archambault and A. B. R. Thomson, unpublished observations, 1985). Accordingly, the present study was undertaken to compare the therapeutic efficacy of cimetidine, 600 mg given twice a day, with that of cimetidine, 300 mg four times a day, in cases of gastroesophageal reflux disease.

This was a multicenter Canadian trial in which eligible patients were randomly selected to receive an eight-week course of open-label cimetidine (Tagamet, Smith Kline & French Canada Ltd), 300 mg four times a day or 600 mg twice a day. Symptomatic improvement was assessed by interview after four and eight weeks of therapy. A repeat endoscopy was done at the eight-week visit.

Patients and Methods

Patient Selection

Patients 18 years and older with endoscopic evidence of esophagitis were considered eligible for the study. Their primary complaint was usually heartburn, defined as a retrosternal burning discomfort occurring during the day, at night or both. Patients were excluded if they had a concomitant gastric or duodenal ulcer or scleroderma. Pregnant and lactating women or those not on a medically acceptable contraceptive regimen were not considered eligible for entry into the study. Patients were also excluded if they had had a gastric operation or vagotomy, a history of significant alcohol abuse or were required to remain on long-term drug therapy, including antineoplastic agents, anticoagulants, metoclopramide, anticholinergics, phenothiazines or thioureas. The occasional use of salicylates, phenylbutazone, indomethacin, benzodiazepines and antacids was permitted and a record of their use was kept. Treatment with H_2-receptor antagonists

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for more than one week before the screening endoscopy excluded potential subjects.

The protocol was approved by the ethics review committee in each participating center. All patients provided written informed consent.

Upon entering, patients were advised to moderate their intake of alcohol, caffeine-containing beverages and tobacco. They were also advised to elevate the heads of their beds 15 cm (6 in) and to avoid stooping and bending after meals. Compliance was checked at each visit by a pill count.

Assessment of Symptomatic Improvement

Symptomatic assessments were conducted at pretreatment and after four and eight weeks of therapy. The average number of episodes and the severity and duration of the worst episode of daytime and nighttime heartburn were assessed using 100-mm visual analogue scales that were completed by the patient. The patient was presented with each question twice in random order. The mean of the two responses was recorded for analysis. The presence and severity of dysphagia, flatulence, nausea and vomiting were assessed by interview, as was the frequency of heartburn after meals and while the patient was bending or lying down.

Endoscopic Assessment of Improvement

Endoscopy was done before treatment and after eight weeks of therapy, usually by the same physician. The appearance of the esophageal mucosa was graded as follows:

Grade 1—normal
Grade 2—hyperemia or opaque mucosa
Grade 3—friability or granular exudate without a discrete lesion
Grade 4—erosions and discrete lesions that cannot be wiped or washed away
Grade 5—ulceration

Grade 2 esophagitis was confirmed by a positive result on a Bernstein test. The appearance of the stomach and duodenal mucosa was also noted. Healing of the esophagitis was defined as grades 3, 4 and 5 resolving to grade 2 or 1, and grade 2 resolving to grade 1. Endoscopic improvement was considered to have occurred if the severity of the esophagitis had declined by at least one grade after eight weeks of therapy.

Statistical Analysis

From the line assessment data of frequency, severity and duration of heartburn, the treatment effect for both regimens was evaluated using the Wilcoxon matched pairs signed-ranks test. The Mann-Whitney U test was used to evaluate any difference between the two regimens. All frequency data were subjected to a χ^2 test, and the Student's t test was used to evaluate differences between the two groups with respect to age, length of illness and duration of relapse. The level of significance was set at $P < .05$.

Results

Patient Population

In total, 153 patients were enrolled in the study. However, 18 patients did not meet acceptable entry criteria and 17 did not complete the eight weeks of therapy: 7 refused to continue through the full eight weeks, 5 had an intercurrent illness, 3 were withdrawn after experiencing an adverse reaction and 3 were removed after two and four days of treatment due to insufficient therapeutic effect. To evaluate the effect of excluding these 35 patients from analysis, the healing rates were recalculated with these patients included as failures. There was no significant change in the interpretation of the results.

TABLE 1.—*Demographic Data of 118 Patients in a Multicenter Canadian Study of Cimetidine Therapy*

Patient Characteristics	Treatment Regimen: Cimetidine 300 mg qid* N = 60	Treatment Regimen: Cimetidine 600 mg bid* N = 58
Age, yr	45.7 ± 14.5	46.0 ± 13.4
Sex ratio, male:female	39:21	44:14
Duration of disease, yr	6.2 ± 6.4	9.4 ± 9.1
Duration of current episode, yr	3.0 ± 5.0	4.1 ± 7.3
Patients who previously used H_2-receptor antagonists, No.	26	24

bid = twice a day, qid = four times a day

*Mean ± standard deviation.

Of the 118 evaluable patients, 60 received cimetidine, 300 mg four times a day, and 58 received cimetidine, 600 mg twice a day. The patient demographics at study entry were similar in both groups (Table 1). There were 83 men and 35 women, aged an average of 45.6 years. About 40% of these patients had received H_2-antagonist therapy for varying periods in the past. Most of the patients had previously used antacids for pain relief and had been given advice about avoiding bending and lifting after meals and elevating the heads of their beds.

Antacid consumption was monitored at each visit and found to be minimal in both groups. Thirteen patients in each regimen occasionally used small amounts of antacids of their choice.

Symptomatic Evaluation

After four weeks of either regimen, there was a significant ($P < .001$) reduction in the number of episodes of heartburn and the severity and duration of the worst episodes of daytime heartburn, as measured by the visual analogue scales (Figure 1). The scores at eight weeks were also significantly lower when compared with pretreatment scores. When the eight-week scores were compared with those obtained after four weeks of therapy, only the 300-mg four-times-a-day regimen provided further significant improvement for the number of episodes ($P < .05$); only cimetidine, 600 mg taken twice a day, produced further significant reduction in the duration of the worst episode ($P < .05$). Both regimens significantly reduced the severity of the worst episode of daytime heartburn. A significant difference between regimens favoring cimetidine, 300 mg taken four times a day, was detected for the severity of the worst episode at eight weeks. There was no statistical difference between the two regimens for any other assessment.

There was also a significant reduction ($P < .001$) in the number of episodes and in the duration and severity of the worst episode of nighttime heartburn after four weeks and eight weeks of therapy when compared with pretreatment (Figure 2). Further significant improvement occurred between four and eight weeks of therapy only for the severity of the worst episode of heartburn and only with the 300-mg

four-times-a-day regimen of cimetidine. At no time was there any difference between regimens in relieving the symptoms of nighttime heartburn.

In all, 24 patients in the 300-mg four-times-a-day group and 20 patients receiving cimetidine, 600 mg twice a day, reported dysphagia on entry into the study. These numbers were reduced to 15 and 6, respectively, after four weeks of therapy, and to 13 and 9, respectively, after eight weeks of cimetidine. The pretreatment incidence of flatulence, nausea and vomiting was low. Improvement occurred over the course of therapy and no difference was found in favor of either regimen.

At pretreatment, 90% of patients receiving 300 mg four times a day of cimetidine and 97% of patients receiving 600 mg twice a day complained of heartburn after meals. Of these, 31 on each regimen reported experiencing these symptoms frequently. After four weeks of therapy, only four patients receiving cimetidine, 300 mg four times a day, and eight patients receiving 600 mg twice a day continued to complain of frequent heartburn. Before entering the study, more than 70% of patients on both regimens of cimetidine complained of heartburn symptoms after bending or lying down. Fewer than ten patients on either regimen complained of frequent symptoms after four weeks of therapy with cimetidine. Symptomatic improvement was maintained at eight weeks. At no time was a difference detected in favor of either regimen in relieving the frequency of heartburn symptoms after meals or while bending or lying down.

Endoscopic Evaluation

At pretreatment, more than 90% of the patients had endoscopic findings of grade 3 esophagitis or worse. The distribution of the endoscopic grading was similar in the two treatment groups (Figure 3). After eight weeks of therapy with cimetidine, there was a dramatic reduction in the proportion of patients with grades 5, 4 and 3 esophagitis. Healing was observed in 57% of patients treated with cimetidine, 300 mg four times a day, and in 55% of patients receiving 600 mg twice a day of cimetidine. No difference was noted between the two treatment groups with respect to the distribution of the endoscopic grades after eight weeks of therapy.

As shown in Figure 3, improvement occurred in all grades of esophagitis. For example, 19 (73%) patients with grade 4 esophagitis receiving cimetidine, 300 mg four times a day, and 21 (88%) patients with grade 4 esophagitis receiving 600 mg twice a day showed improvement endoscopically with treatment. Of these, 17 (65%) receiving 300 mg four times a day and 19 (79%) receiving 600 mg twice a day were considered healed. Worsening of the endoscopic grade occurred only in the group of 26 patients presenting with grade 3 esophagitis. Three receiving 300 mg four times a day and one receiving 600 mg twice a day had worsening of the endoscopic grade. The demographic data for these patients did not differ significantly from the rest of the patient population.

A total of 36 patients had associated gastritis, duodenitis or both; 35 (97%) of these had grade 3 esophagitis or worse. After eight weeks of therapy, the gastritis or duodenitis had healed in 29 patients (81%). These lesions failed to heal in

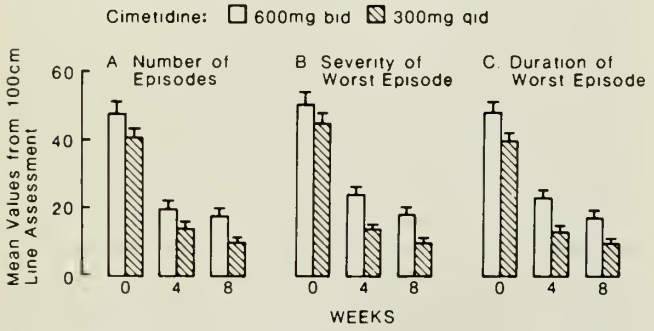

Figure 1.—Symptomatic evaluation of daytime heartburn. bid = twice a day, qid = four times a day

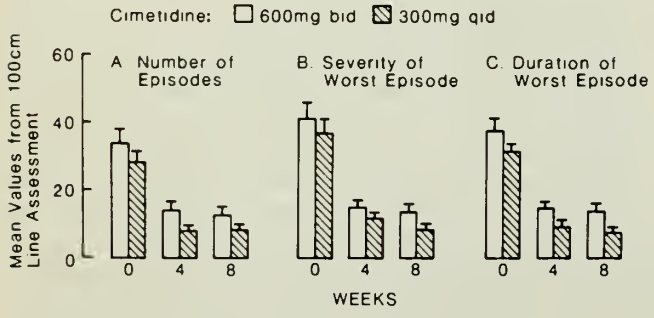

Figure 2.—Symptomatic evaluation of nighttime heartburn. bid = twice a day, qid = four times a day

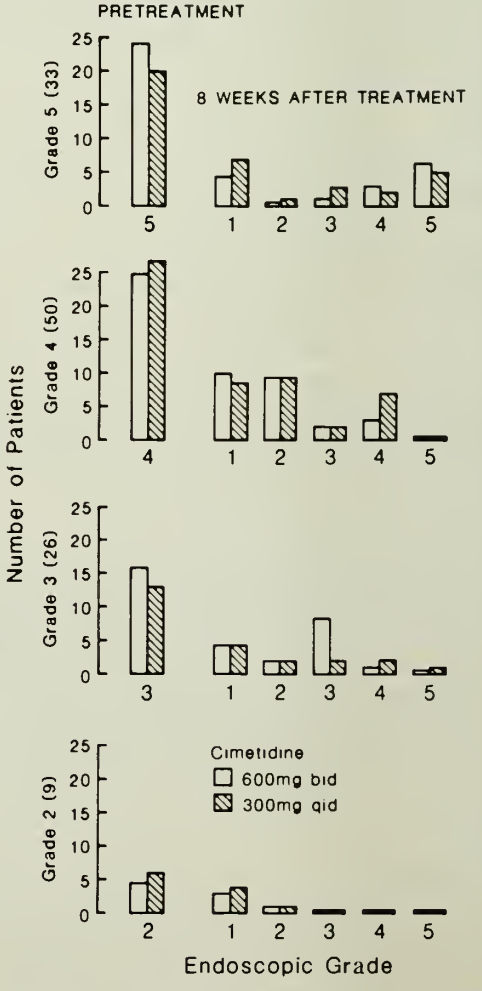

Figure 3.—Endoscopic evaluation at pretreatment and after eight weeks of treatment. bid = twice a day, qid = four times a day

seven patients: in three patients receiving cimetidine, 300 mg four times a day, and in four patients treated with 600 mg twice a day. In four of the seven patients in whom neither the gastritis nor the duodenitis resolved, the esophagitis also did not heal.

Adverse Reactions Reported

Adverse reactions reported by investigators as being possibly related to therapy are shown in Table 2. Four patients taking cimetidine, 300 mg four times a day, and six patients treated with cimetidine, 600 mg twice a day, complained of adverse reactions. In one person gynecomastia developed after six weeks of treatment. In general, the incidence of adverse reactions was low, and no unusual or unexpected adverse reactions were reported with the use of 600 mg twice a day of cimetidine.

TABLE 2.—*Adverse Reactions Reported*

Cimetidine Dosage	*Reaction to Therapy*	*No. Subjects Reporting*	*Comments*
300 mg qid	Headache	1	Resolved on therapy regimen
	Dizziness, forgetfulness, nausea, weakness	1	Discontinued study
	Loss of libido	1	Resolved poststudy
	Impotence	1	Resolved poststudy
600 mg bid	Rash	2	1-Discontinued study 1-Resolved poststudy
	Diarrhea	1	Resolved on therapy regimen
	Dizziness, general weakness	1	Discontinued study
	Gynecomastia	1	Discontinued study
	Slow pulse	1	Outcome unknown

qid = four times a day, bid = twice a day

Discussion

The pathogenesis of gastroesophageal reflux disease is complex and multifactorial.[1-7] Attention has focused for many years on the incompetence of the lower esophageal sphincter high-pressure zone. Recently, however, interest has been directed to the acid-clearance mechanism, the resistance of the esophageal mucosa, the volume and concentration of acidic gastric juice, duodenal-gastric reflux and the rate of gastric emptying. Furthermore, studies in patients with gastroesophageal reflux disease are difficult both to conduct and to interpret because of the multiple pathogenic mechanisms and the numerous clinical approaches to defining the disorder.[8] The condition may be defined on the basis of symptoms, abnormalities in gross appearance of the esophagus at endoscopy, abnormalities in the esophageal mucosal biopsy specimen, a positive Bernstein test or an abnormal motility pattern.[9] As a result of this complex interplay,[3,10] it must be stressed that in this study we are likely dealing with a heterogenous group of patients.

To date, the use of cimetidine has been reported in numerous trials involving more than 700 patients with gastroesophageal reflux disease (Table 3). The definition of gastroesophageal reflux disease varied from study to study. In addition, the severity of reflux disease varied greatly; in some studies patients had symptomatic reflux without endoscopic signs of esophagitis, whereas in others the patients had severe esophagitis, ulceration or stricture. Patients were treated for periods varying from 4 to 12 weeks with doses of cimetidine varying from 1 to 2 grams per day. In 13 of these 18 (72%) studies, there was significant improvement in the patients' symptoms in the cimetidine-treated groups (Table 3). In 7 of 14 (50%) studies, there was endoscopic improvement and in 3 of 7 studies (43%), the short-term treatment of esophagitis was associated with improvement histologically. There was generally no correlation among the improvement in the patients' symptoms or endoscopic or histologic findings. For example, there was endoscopic and histologic but not symptomatic resolution in the study of Wesdorp and co-workers,[11] whereas symptomatic and histologic but not endoscopic improvement occurred in the study of Fiasse and associates.[12] Of the seven studies showing a significant improvement in the endoscopic appearance of the esophagus in patients treated with cimetidine, five reported symptomatic improvement. We should stress that in all of these studies, patients had free access to antacids, and patients taking cimetidine often consumed less antacid than did patients taking a placebo. None of the studies had pretreatment stratification for smoking or for obesity. Our study adds 118 more patients with esophagitis in whom improvement in the symptoms of gastroesophageal reflux disease was noted with the use of cimetidine (Figures 1 and 2). In more than half of the patients healing was observed endoscopically after eight weeks of therapy (Figure 3). With both therapeutic regimens—cimetidine, 600 mg twice a day and 300 mg four times a day—the diminution in daytime and nighttime pain was gratifying.

Other authors stress the possible role of cimetidine in resolving mucosal sensitivity, as assessed by the acid perfusion test, esophageal manometry or overnight pH monitoring. Two studies reported significant cimetidine-associated improvement by pH monitoring.[22,29] One reported significant improvement[30] and three reported no improvement in the results of the Bernstein test.[10,11,18] None of the three studies using manometry showed improvement as a result of treatment with cimetidine.[11,18,21]

This randomized trial did not include a placebo group. However, numerous previous placebo-controlled studies have shown a superiority of cimetidine therapy over placebo for the symptomatic improvement of gastroesophageal reflux disease, whereas half of the studies showed improved endoscopic findings (Table 1). In view of the proven benefit of cimetidine therapy in patients with gastroesophageal reflux disease (Table 3) and the fact that almost half of the patients entered in this study had benefited from cimetidine use in the past, it was considered unacceptable to withhold this therapy and thereby have a group of placebo-treated "control" subjects. The results obtained in this study, however, are comparable with those observed in the cimetidine-treated patients reported by others. For example, a placebo-controlled study reported by Bennett and colleagues[25] showed a significant reduction in night pain in 51 patients treated with 1 or 2 grams of cimetidine daily for six weeks, as compared with 33 patients treated with placebo plus antacids. Antacid consumption was reduced by about 50% in the cimetidine-treated patients. In a large multicenter placebo-controlled study involving 94 persons with gastroesophageal reflux disease, Behar and colleagues[13] compared the efficacy of cimetidine therapy, 300 mg given four times a day for eight weeks. The

improvement in symptomatology and reduced antacid use was superior to that noted in the placebo-treated patients: the average number of episodes of daytime pain declined in the cimetidine group from about five to two, and the average number of episodes of nighttime pain declined from two to less than one. While this symptomatic improvement in the cimetidine-treated groups noted in these two studies was comparable with the results observed in our study (Figures 1 and 2), cimetidine therapy did not improve the endoscopic appearance of the esophagitis in the study of Behar and coworkers,[13] whereas endoscopic improvement was noted in our study (Figure 3). In our study, both treatment groups showed similar symptomatic improvement between pretreatment and four weeks and between pretreatment and eight weeks (Figures 1 and 2).

From the patients' perspective, the dramatic improvement in symptoms was welcome, and treatment was considered to be overall successful. The incidence of side effects in patients taking the usual total daily dose of 1,200 mg of cimetidine is low.[30] We also noted a low incidence of side effects (Table 2). This was a short-term study, however. It is possible that some patients might have a recurrence of symptoms and possibly a worsening of their esophagitis once treatment with H_2-receptor antagonists has been discontinued. In this study we did not address the important question of the possible need for low-dose maintenance therapy with cimetidine to prevent recurrence of disease.

Sonnenberg and associates[31] examined 30 patients with gastroesophageal reflux and esophagitis treated for 6 to 12 weeks with 1.6 grams per day of cimetidine. The mucosal defects healed in 6 patients, improved in 14 and remained unchanged in 10. Lower esophageal sphincter pressure, acid clearance, results of the acid perfusion test and histologic signs of mucosal infiltration did not improve after healing of the mucosal defects. It is of concern that both in the previous study of Sonnenberg and co-workers[31] and in our study, about a third of the patients with grade 5 endoscopic esophagitis had no improvement during eight weeks of therapy with cimetidine. The persistence of these abnormalities might explain the tendency of esophagitis to recur after symptomatic and endoscopic "healing." It has been suggested that longer periods of therapy might be needed to achieve healing or to prevent the recurrence of esophagitis.[31] However, treating patients with gastroesophageal reflux disease for 12 months with ranitidine therapy failed to achieve further symptomatic, endoscopic or histologic improvement beyond that achieved after eight weeks of treatment.[26]

Accepting the variations in the definition of gastroesophageal reflux disease, the variable endpoints and the likely heterogeneity of the patients, what improvement might we reasonably expect for our patients treated with cimetidine? Significant symptomatic improvement was reported in about two thirds of the studies presented in Table 3. Of the studies using endoscopy, a third reported significant endoscopic improvement with the use of cimetidine. Histologic findings significantly improved in a third of the studies addressing this variable. Patients will likely consume less antacid while taking cimetidine, but there is unlikely to be a consistent change in the results of the Bernstein test, pH monitoring or esophageal manometry.

TABLE 3.—*H_2-Receptor Antagonists in Treatment of Gastroesophageal Reflux Disease*

Study Source		Number of Patients	Symptoms*	Significant Effect* Endoscopy	Histology	Antacid	Tests†
Cimetidine Therapy							
1978	Wesdorp et al[11]	24	−	+	+	−	B−,M−
	Behar et al[13]	94	+	−	...	+	B+
	Powell-Jackson et al[14]	27	+	−	−	+	B−
1979	Brown[15]	22	+	+	+	+	...
	Ferguson et al[16]	20	−	+	−	−	...
	Lepsien et al[17]	36	+	−	−	+	...
		22‡	+	+	...	+	...
	Petrokubi and Jeffries[18]	15	+	+	...	+	M−
1980	Bright-Asare and El-Bassoussi[10]	50	−	−	...	...	B−,M−
	Festen et al[19]	20	−	−	...	−	...
	Fiasse et al[12]	34	+	−	+	+	...
	Druguet and Lambert[20]	82	+	+	...	−	...
	Thanik et al[21]	43	+	+	...	−	...
	Bennett et al[22]	68	+	...	...	+	pH+
		18‡	−	...	...	...	pH−
1981	Greaney and Irvin[23]	20	−	−	...	...	...
1982	Bradby et al[24]	43	+	...	−	...	...
1983	Bennett et al[25]	84	+	...	...	+	pH+
Total		722					
Ranitidine Therapy							
1982	Sherbaniuk et al[26]	73	+	+	−	+	
1982	Berstad[27]	168	+	+	−	+	
1983	Wesdorp et al[28]	36	+	+	+	+	
Total		277					

*The symbol + signifies that significant improvement occurred, − indicates that there was no significant improvement.
†B = Bernstein test, M = esophageal manometry and pH = pH monitoring.
‡Two groups of patients were reported.

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Nosocomial Pneumonia in Patients in Intensive Care Units

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Nosocomial pneumonia is a major cause of mortality among patients in intensive care units, despite recent advances in antimicrobial therapy. Aerobic Gram-negative bacilli remain the pathogens responsible for most of these pneumonias. These organisms colonize the oropharynx of severely ill patients, and their subsequent aspiration results in lower respiratory tract infection. Recent investigation into the pathogenesis of oropharyngeal bacterial colonization has shown the central importance of bacterial adherence mechanisms.

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Sophisticated therapies in intensive care units allow many patients to survive a primary illness, only to succumb to nosocomial infection. Pneumonia is now the most common hospital-acquired infection leading to death, occurring in 0.5% to 5% of all in-hospital patients and in 12% to 15% of patients ill enough to require intensive care.[1-3] The incidence of pneumonia in the intensive care unit (ICU) setting is related to the primary disease process; rates of 5% for patients with cardiovascular disease, 24% for primary respiratory tract disease and 63% for acute respiratory failure have been reported.[2,4]

Gram-negative bacilli (GNB) are the pathogens responsible for nosocomial pneumonia in 75% to 90% of cases, with *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli* and *Proteus* species the most commonly isolated agents.[1,5,7] In a study of patients in ICUs, pneumonia due to Gram-positive cocci did not add significantly to the usual mortality of 4% to 5%, while that caused by GNB resulted in a mortality of 33%; a 70% mortality occurred if *P aeruginosa* was present.[8] Anaerobic bacteria have not been recovered despite careful techniques in two recent studies of nosocomial pneumonia.[9,10] In this review we will address recent advances in the attempt to diagnose, treat and prevent these increasingly important bacterial infections. *Legionella* species have been noted to cause epidemic nosocomial pneumonia in certain hospitals. In most intensive care units, however, *Legionella* species and other newly recognized agents that may be responsible for nosocomial pneumonia constitute less than 5% of all cases and will not be discussed here.[11-15]

Pathogenesis

An alteration in bacterial colonization of the oropharynx is the most important factor responsible for the increased incidence of and change in the bacterial species responsible for pneumonia in patients in ICUs. In a baboon model of acute respiratory failure, 9 of 11 animals were shown to have GNB oropharyngeal colonization before the onset of GNB pneumonia.[16] As many as 90% of patients in ICUs in whom pneumonia develops have an earlier oropharyngeal colonization with the same species of GNB.[1,2] Pneumonia develops in 12% to 25% of all patients so colonized, whereas only 3% of patients not previously colonized have this complication.[2]

The risk of colonization of the pharynx with GNB is related to the general state of health of the population studied. Gram-negative bacilli are rarely cultured from the oropharynx of healthy persons.[17-19] In experimental animals, starvation for three days results in a pronounced increase in GNB colonization.[20] A third of healthy patients become colonized with GNB 48 hours after a major surgical procedure.[21] About 17% of moderately ill and 55% of severely ill patients are colonized at the time of admission to an ICU.[17] Acute respiratory failure is associated with an especially high risk of GNB colonization and pneumonia. In all of the animals in a recent study of a model of the adult respiratory distress syndrome, GNB oropharyngeal colonization and subsequent pneumonia developed.[16] In all, 74% of patients who die of the adult respiratory distress syndrome have histologic proof of pneumonia at autopsy.[22] Specific risk factors for colonization include coma, acidosis, alcoholism, diabetes mellitus, hypo-

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ABBREVIATIONS USED IN TEXT
GNB = Gram-negative bacilli
ICU = intensive care unit
TPC = telescoping protected [brush] catheter

tension, leukocytosis, leukopenia, azotemia, primary respiratory tract disease, endotracheal intubation and possibly the prophylactic use of antibiotics.[2,23,24] The duration of ICU stay is not a significant risk factor for colonization, as the majority of patients who become colonized do so by the fourth hospital day. Sources of the GNB appear to be gastrointestinal organisms endogenous to a colonized patient and GNB transmitted from other patients by hospital personnel.[25]

Bacterial adherence to epithelial cells is of central importance to the pathogenesis of oropharyngeal GNB colonization, a phenomenon previously found in patients with urinary and gastrointestinal tract infections.[26,27] Gram-positive organisms normally colonize the oropharyngeal area and may protect against adherence and colonization by GNB. Patients who become colonized have fewer Gram-positive cocci and larger numbers of GNB adherent per epithelial cell.[21]

Fibronectin, a 200,000-dalton cell surface glycoprotein, may be the factor regulating GNB adherence and colonization. Gram-positive cocci bind well to cells rich in fibronectin, whereas GNB bind well only to cells that are fibronectin deficient.[28,29] GNB attach to sugar-containing sites on the cell membrane by means of fingerlike projections on their surface called pili. Fibronectin probably protects against GNB adherence by blocking these sites.[30,31] Trypsinized oropharyngeal cells from healthy volunteers and unmodified cells taken from GNB-colonized patients are both remarkable for decreased concentrations of cell surface fibronectin, as well as an increased ability to bind GNB.[31,32] A prospective study of healthy patients undergoing elective surgical procedures showed an increase in salivary protease activity following the operation, accompanied by a decrease in cell surface fibronectin and an increased *Pseudomonas*-cell binding ratio.[33] It is not clear whether salivary protease activity is augmented by host or microbial sources or by a decreased amount of a normally present protease-inhibitor.

The ICU environment also may be important in the pathogenesis of nosocomial pneumonia. Potential colonization of respiratory support equipment has been shown as an important, yet preventable, source of this nosocomial infection.[1,5,34,35] Invasive catheters and urinary drainage devices allow a nidus of lymphohematogenous spread of infection, although this remains a relatively uncommon cause of pneumonia.[1,2] In an autopsy series of patients with the adult respiratory disease syndrome, however, a third of the cases of pneumonia found were felt to be secondary processes, with peritoneal abscesses the most common primary site of infection.[22] Interpatient transfer of bacteria by hospital personnel, including poor hand-washing patterns by physicians, may result in an increased incidence of infection with resistant organisms.[36]

Diagnosis

Even if a nosocomial pneumonia is suspected on the basis of fever, leukocytosis and a new infiltrate on chest radiography, the presence of infection is not certain. In two recent studies, the use of clinical and radiologic signs and the response to therapy to diagnose the presence of pneumonia in patients with diffuse lung injury resulted in a 30% to 45% incidence of false-positive and false-negative diagnoses.[22,37] Thus, most clinicians initiate antibiotic therapy upon any suspicion of nosocomial pneumonia, given the risks of untreated infection. Diagnostic methods are most useful for identifying an organism responsible for the pneumonia in order to guide specific therapy. Numerous authors have reviewed the use of various diagnostic techniques toward this goal.[1,5,38-41] While bacteria are the most common etiologic agents in nosocomial pneumonia, patients with certain malignant lesions, those with neutropenia and patients taking immunosuppressive medications or with congenital or acquired immunocompromising diseases are at additional risk for pneumonia caused by a wide spectrum of opportunistic organisms. Indeed, pneumonia is the most common site of serious infection in these hosts. The additional complexity involved in isolating and treating the fungi, viruses and parasites that can infect these patients often requires a more aggressive diagnostic approach. Readers are referred to several excellent reviews of pneumonia in an immunosuppressed host, and we will focus on cases of generally immunocompetent patients.[39-45]

The initial diagnostic intervention should be to obtain specimens for culture from sites that are most likely to provide a definitive diagnosis. Several blood specimens should be obtained for culture. If pleural fluid is present in sufficient quantity to be safely aspirated, it should be examined by Gram's stain and culture. If an organism is identified from these sources, therapy can then be specifically directed. Unfortunately, the use of expectorated sputum to identify an infectious agent may not be reliable, as it is virtually impossible to separate bacteria that colonize the oropharynx from those responsible for the pneumonia. Expectorated sputum is often not representative of lower respiratory tract secretions.[46,47] Methods of "grading" the quality of expectorated sputum and quantitative culture techniques have not proved accurate in patients in ICUs.[41,46-50] Sputum obtained by transtracheal aspiration or by suction (nasotracheally or through a tracheostomy or endotracheal tube) theoretically allows sampling of tracheal secretions without oropharyngeal contamination. Although transtracheal aspiration has been extensively studied in cases of community-acquired pneumonia,[49-55] it has not been selectively studied in patients with hospital-acquired infection. Also, both suctioned sputum and transtracheal aspirate may be contaminated with a tracheacolonizing flora, which may not represent the cause of the pneumonia.[49,51,56-58]

In recent studies new techniques have been used to bypass the upper respiratory tract and thus obtain uncontaminated lower tract secretions. Specimens taken by brushing and suctioning using standard fiberoptic bronchoscopy are frequently contaminated by bacteria that colonize the oropharynx.[59-62] The combination of quantitative cultures and immunofluorescent staining techniques was recently found to significantly increase the sensitivity and specificity of cultures obtained in this fashion.[63] As few patients were receiving antibiotics and few had other bacteriologic proof of pneumonia, further evaluation of these techniques is needed in an ICU population before they can be recommended.

A "wedged" catheter technique for use in intubated patients has recently been evaluated in cases of community-acquired pneumonia, with encouraging results.[64] Controlled studies in patients with hospital-acquired pneumonia are needed before this technique can be recommended in the ICU population. The telescoping protected brush catheter (TPC) inserted through a fiberoptic bronchoscope has recovered sterile lower tract secretions in healthy patients.[59,60,65] Because low concentrations of oropharyngeal organisms can be taken from the lower respiratory tract of some healthy volunteers, quantitative culture techniques are important when using the TPC.[9,61,62,66] In a comparison of diagnostic techniques using a dog model of pneumococcal pneumonia, the TPC showed a sensitivity and specificity second only to transthoracic lung puncture.[56] In patients with community-acquired pneumonia, TPC recovered the same organisms found in all bacteremic patients.[67] In a study of primates with nosocomial pneumonia, the TPC was 70% sensitive and 90% specific.[10] Further evidence of the sensitivity of this technique is provided by a recent study that compared quantitative cultures of specimens obtained with the TPC and by lung biopsy in patients who died while on mechanical ventilation. All specimens were obtained immediately after the death of the patient. TPC cultures identified every bacteria present in every patient with histologic proof of pneumonia. There were some false-positive culture results, but no case of pneumonia was missed with the TPC.[9] Unfortunately, a recent comparison of the TPC, transthoracic lung puncture and the use of a regular cytology brush in patients with underlying diseases admitted for acute pulmonary infections had less encouraging results.[68]

Thus, studies of various techniques of obtaining specimens by fiberoptic bronchoscopy have yielded variable results or the techniques have not been adequately tested in ICU patients. Further, although fiberoptic bronchoscopy is a safe procedure in ambulatory patients,[69] its use in critically ill patients often results in a higher rate of complications.[70] For these reasons, most physicians do not routinely use these techniques.

More invasive diagnostic modalities—direct lung aspiration and open-lung biopsy—have been studied predominantly in immunocompromised hosts.[3,39-44,49] These procedures carry a significant risk of complications, and no data are available to support their use in nonimmunosuppressed ICU patients.

Clinical Approach and Therapy

In a patient with presumed nosocomial pneumonia and no pathogen seen on Gram's stain of a pleural fluid specimen, sputum is the only material available on which to make therapeutic decisions. Although sputum is often contaminated with organisms not responsible for the nosocomial pneumonia, careful evaluation of a Gram's stain may indicate the need for broader antimicrobial coverage if an unsuspected pathogen such as *Hemophilus influenzae* is seen. This organism is a small Gram-negative coccobacillus that may cause community- or hospital-acquired pneumonia.[9,64] If blood, pleural fluid and sputum specimens are not diagnostic, the clinician must decide whether or not to proceed to more invasive diagnostic procedures. One or more of these procedures may be helpful in the initial diagnosis or after failure of empiric therapy. Each procedure has risks, and the physician must weigh the possible morbidity against the probabilities of obtaining useful therapeutic information. In most instances, the initial choice of antimicrobial therapy is empiric.

Recommended empiric therapy is the use of two antimicrobial agents to cover the wide spectrum of organisms (with variable antimicrobial resistance) responsible for nosocomial pneumonia. The combination of an aminoglycoside with an extended-spectrum penicillin or a cephalosporin will accomplish these goals in most instances.[71-75] An apparent *H influenzae* on sputum Gram's stain mandates coverage of this organism as well. Third-generation cephalosporins may offer improved coverage of GNB with less nephrotoxicity than aminoglycosides. Cefotaxime sodium and cefoperazone sodium may be the most useful of this group for the treatment of patients with hospital-acquired pneumonia (Table 1).[73-78] In a recent trial, cefotaxime was found to be more effective and less toxic than the combination of nafcillin sodium and tobramycin in treating patients with serious bacterial infections.[78] Further studies are required, however, before single-drug empiric therapy can be recommended for patients with hospital-acquired pneumonia. Suspected infection with *P aeruginosa* (as in hospital epidemics) requires additional coverage with an extended-spectrum penicillin or cefoperazone.[70-74] At this time, more specific choices of antimicrobial drugs cannot be generalized from the literature. The bacterial flora of each hospital and its antimicrobial sensitivities should be used as a guide in making individual drug decisions. Unfortunately, the previously noted high mortality rates for Gram-negative nosocomial pneumonia occur in spite of antimicrobial therapy.[8,72,73]

If a pathogen is subsequently cultured from blood or pleural fluid specimens, specific antimicrobial therapy may be used and inappropriate agents dropped from the regimen. Efficacy of antibiotic therapy in patients with bacteremia may be predicted by measuring peak serum bactericidal concentra-

TABLE 1.—*Third-Generation Cephalosporins Useful in Empiric Therapy for Nosocomial Pneumonia*

Drug Name	*Excretion*	*IV Dose in Adults*
Cefoperazone sodium . .	Biliary	2 grams q 4-12 h*
Cefotaxime sodium	Renal	2 grams q 4-6 h*

IV = intravenous

*In treating severely ill patients, both drugs should be given every 4 h.

TABLE 2.—*Aminoglycoside Plasma Concentrations Associated With Improved Response in Cases of Gram-Negative Pneumonia**

Drug Therapy†	*1-H Postinfusion Plasma Levels*	
	Maximal Peak μg/ml	Mean Peak μg/ml
Gentamicin sulfate/tobramycin . .	≥ 7	≥ 6
Amikacin sulfate	≥ 28	≥ 24

*From Moore et al.[80]

†Aminoglycosides were used in combination with a penicillin or cephalosporin in fixed doses.

tions.[79] Achieving certain peak aminoglycoside levels has been shown to improve the outcome of patients with GNB pneumonia (Table 2).[80] Although results of culture of expectorated or suctioned sputum may be used to initiate broader antimicrobial coverage, they are not reliable enough alone to allow discontinuation of empiric coverage.

In a single study, endotracheally administered sisomicin sulfate, in addition to standard intravenous antibiotic therapy in patients with nosocomial GNB pneumonia, resulted in a decrease in mortality without toxic effects or emergence of drug-resistant organisms.[81] Systemic levels of sisomicin were not affected by the endotracheal dose, suggesting the importance of antibiotic concentration locally in determining the efficacy of therapy.[82] Confirmation of these results is necessary before this therapy can be recommended.

Prevention

Although effective infection control measures cannot prevent oropharyngeal colonization of susceptible patients, they may prevent GNB already resistant to antimicrobials from entering a patient's environment. These methods include hand-washing after contact with each patient and proper sterilization of respiratory therapy equipment.[1,34,36]

Because most cases of nosocomial pneumonia are preceded by oropharyngeal colonization with Gram-negative bacteria (GNB), research has focused on preventing such colonization. Trials of the prophylactic use of parenteral antibiotics to prevent hospital-acquired pneumonia resulted in the emergence of antibiotic-resistant organisms.[83] Efforts were next directed at prophylactically using antibiotics locally in the oropharyngeal region. Even minimal doses of antibiotics can alter the structure and function of bacterial "adhesins" (bacterial structures involved in binding to cells) and thereby prevent bacterial-cellular binding.[84,85] Between 1970 and 1975, three trials using prophylactic polymyxin B sulfate aerosolized into the oropharynx of ICU patients showed a significant decrease in colonization with GNB.[86-88] One trial of continuous polymyxin B use resulted in pneumonias caused by predominantly polymyxin-resistant bacteria. No trial showed a significant decrease in mortality. An additional three trials using endotracheally administered gentamicin sulfate to prevent infection in patients with tracheostomies resulted in no improvement in overall mortality.[89-91] Unfortunately, there was a significantly increased incidence of gentamicin-resistant organisms in the antibiotic-treated groups. Aerosolized gentamicin had no effect on infectious complications or mortality in a prospective randomized study of patients with inhalation burn injuries.[92] In a recent study of acute respiratory failure in animals, the combination of intensive oropharyngeal suctioning, topical polymyxin B and systemic ampicillin lowered the attack rate of GNB pneumonia to 19%, compared with 100% in control animals. Overall mortality was not stated, and ampicillin therapy was begun before respiratory failure. However, these findings support the rationale for altering the oropharyngeal environment in seriously ill patients.[16]

Early trials of an anti-*Pseudomonas* vaccine were effective in lowering the prevalence of *Pseudomonas* colonization and infection in susceptible patients, but there was no effect on mortality.[93-96] A newer anti-*Pseudomonas* vaccine has shown more encouraging results in burn patients.[97-98] A human vaccine composed of the core lipopolysaccharide shared by most clinically important GNB had significant protective effect in immunosuppressed animals.[99] Passive immunization using human antiserum produced by vaccinating healthy volunteers decreased mortality in patients with GNB bacteremia.[99,100] Unfortunately, it will require more investigation before these techniques are available for use and proved to be effective in patients in ICUs.

Other methods to prevent colonization by Gram-negative bacteria will use knowledge gained from studying bacterial adherence. Future therapeutic modalities may involve isolated cell receptor analogues or isolated bacterial adhesin analogues to interfere in the binding process. Alternatively, the increased protease activity in saliva of colonization-susceptible patients could be neutralized to prevent the loss of fibronectin, or a method to restore already lost fibronectin may be developed.

Summary

Nosocomial bacterial pneumonia remains a major cause of mortality in ICU patients. In patients not responding to empiric therapy, new diagnostic techniques involving bronchoscopically placed protected catheters may allow more specific isolation of causative agents and may thereby improve the efficacy of current antibiotic therapy. Future advances in this field should focus on preventing these infections, using knowledge gained from an orderly sequence of recent investigations. These studies have shown that severe illness results in a loss of fibronectin from oropharyngeal cell surfaces. GNB colonization follows, and aspiration of oropharyngeal bacteria leads to GNB pneumonia. Using this knowledge at a molecular and cellular level may allow interruption of GNB colonization and thereby GNB pneumonia. Alternatively, future vaccines may provide effective prophylaxis against these infections.

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ON RATIONING OF HEALTH CARE

As rising health expenditures in the United States constitute a growing proportion of the nation's economic output, driven by factors such as the development of improved medical technology and the aging of the population, public policymakers are reassessing the scope of government health care financing in light of competing public funding priorities. Actions already initiated to limit or reduce economic resources allocated to health care have given rise to the possibility that some form of explicit rationing of medical services may be forced upon society in the near future. Resource allocation decisions made by government and other third-party payors may cause drastic cost-cutting measures within the health care delivery system, which in turn may result in the rationing of services to patients as the availability of or access to those services is diminished.

Practicing physicians are faced with the dilemma of attempting to serve the societal goals of high quality medical care, equity of access to care and health care cost containment—goals that may in fact conflict with one another. Pressures exerted by hospitals, government and third-party payors threaten to cast physicians as agents of rationing in strategies intended only to curtail escalating health care costs.

Given the far-reaching ethical, political and social implications of policies concerning the rationing of scarce medical resources, decisions in this regard must be reached through a process involving full participation by all concerned sectors of society. Physicians, by virtue of their medical expertise and their central role in the health care delivery system, must play an important role in the development of such a broad-based consensus, but cannot be expected to assume total responsibility for the equitable disbursement of society's limited health resources. The medical profession does, however, have a clear responsibility in helping to obviate, to the greatest possible extent, the necessity of explicit rationing schemes. Efforts toward this end include the promotion of technology assessment to develop information on the benefits and costs of alternative treatments, the elimination of inappropriate or unnecessary treatments and procedures, better communication with patients regarding the relative benefits and costs of alternative interventions and utilization of the least expensive settings for the safe and efficient delivery of high quality medical care. Incorporation of greater emphasis on preventive medicine in clinical practice also must be encouraged as an appropriate cost-containment measure.

While the medical profession cannot abdicate its responsibility to society in addressing the need to control health care costs, the individual physician's primary and overriding responsibility is to his or her patients. In the care and treatment of patients, a physician must be guided by decisions based on the informed consent of patients to whatever therapies are clearly and proportionately beneficial to them. A physician has a duty to serve as an advocate of the patient's best interests and ought not become the sole responsible agent of institutional rationing schemes based on strictly fiscal considerations.

A policy statement from the Committee on Evolving Trends in Society Affecting Life, California Medical Association

Adopted by the CMA Council, August 23, 1985

Argon Laser Treatment of Strawberry Hemangioma in Infancy

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Argon laser therapy is effective for removing port-wine stains and for reducing cutaneous vascular and pigmented lesions. Strawberry hemangiomas, being much thicker lesions than port-wine stains, were considered not appropriate for argon laser treatment. Using argon laser therapy in 13 cases of strawberry hemangioma, we achieved poor to dramatic results.

(Achauer BM, Vander Kam VM: Argon laser treatment of strawberry hemangioma in infancy. West J Med 1985 Nov; 143:628-632)

Since early 1970 argon laser therapy has been the most effective for removing port-wine stains, the blue green light (488 to 520 nm) corresponding with the maximum absorption of both hemoglobin and melanin. The argon laser has been useful for reducing cutaneous vascular and pigmented lesions. Laser light penetrates intact epidermis—usually at less than 1 mm—until its energy is absorbed by the lesion.

Strawberry hemangioma, the most common vascular tumor seen in infancy, is distinguished by its tendency to involute.[1] The strawberry lesion usually presents as a flat lesion a few days after birth. Growth may be rapid, with maximum size generally being reached at about one year. The lesion is characterized by its bright red color, raised texture and lobular appearance.[2] Strawberry marks are somewhat more common in premature infants, and there is a greater incidence in female than male infants. About 50% of the lesions regress by age 5 years and 70% by age 7.[3] Strawberry hemangiomas are much thicker lesions than port-wine stains and, therefore, theoretically not ideal for argon laser treatment.

Apfelberg and co-workers reported three cases treated by the argon laser and noted cessation of rapid growth and induction or resolution.[4] Hobby reported six cases treated, with improvement in all cases.[5] Argon laser therapy has been established as the treatment of choice for port-wine hemangiomas, but is relatively contraindicated for port-wine stains in children because of the greater risk of scarring.[6]

Hobby postulated that the laser treatment might be used when the lesion is first noted, before it has time to grow.[5] If these lesions could be treated before attaining significant size, deforming, complicated tumors may be totally prevented. Our encouraging experience with 13 patients treated with the argon laser is presented.

Materials and Methods

The Cooper Medical 770 argon laser was used with a 2-mm fiberoptic hand-held wand. Depending on the size and density of the lesion, 1.0 to 2.0 W was delivered. When the eyelid was involved, protective eye shields were inserted into the eye after the instillation of topical ophthalmic anesthetic. All persons in the room wore protective eye covering. Treatments were done on an outpatient basis under local or, in two cases, general anesthesia. Both ethyl chloride and 1% lidocaine (Xylocaine) hydrochloride without epinephrine were used as local anesthetic agents. The wand was held about 1.5 cm from the lesion and advanced over the lesion as blanching occurred. Antibiotic ointment and sterile dressing were then applied to treated areas.

Posttreatment results were evaluated and categorized as excellent to essentially good, good to 50% improved, fair to 25% to 50% smaller or poor to less than 25% changed or with complications. Patient information, indications for treatment, details of treatment and results are presented in Table 1.

Discussion

Despite the fact that strawberry hemangiomas may involute, there are medical and occasional psychological indications for treatment before spontaneous involution. When the

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TABLE 1.—*Clinical Features and Results of Argon Laser Treatment in 13 Patients With Strawberry Hemangioma*

Patient	Age (mos)	Sex	Indication	Location	Size (cm)	Watts Delivered	Time (sec)	Results	Follow-up (mos)
1	11	M	Bleeding	Scalp	2.5 x 2.5	1.6	87	Excellent	12
2	10	F	Speech	Lip	2.0 x 2.0	1.8	108	Fair	12
3	5	F	Bleeding	Groin	5.0 x 0.7	1.8	506		
					1.8 x 1.6	1.6	231*	Excellent	10
4	2½	M	Growth	Shoulder	5.0 x 5.0	1.8	506	Fair	9
5	5	F	Bleeding	Lip	2.5 x 2.5	1.8	136	Fair	6
6	12	F	Growth	Shoulder	4.0 x 4.0	1.8	443	Good	6
7	24	M	Speech	Lip	2.0 x 4.0	1.8	284	Good	5
8	36	F	Vision	Face	5.5 x 8.0	1.8	212		
						1.8	512*	Good	4
9	6	M	Growth	Forehead	1.5 x 2.5	1.8	57	Excellent	3
10	12	F	Bleeding	Neck	20.0 x 30.0	1.8	593	Poor	2
11	5½	F	Vision	Eyelid	2.5 x 2.5	1.8	32	Excellent	2
12	6½	F	Ulceration	Neck	2.5 x 2.5	1.8	162	Good	1
13	3	F	Bleeding	Nose	3.75 x 3.75	1.8	. . .	Poor	3

*Case treated with two-stage laser application.

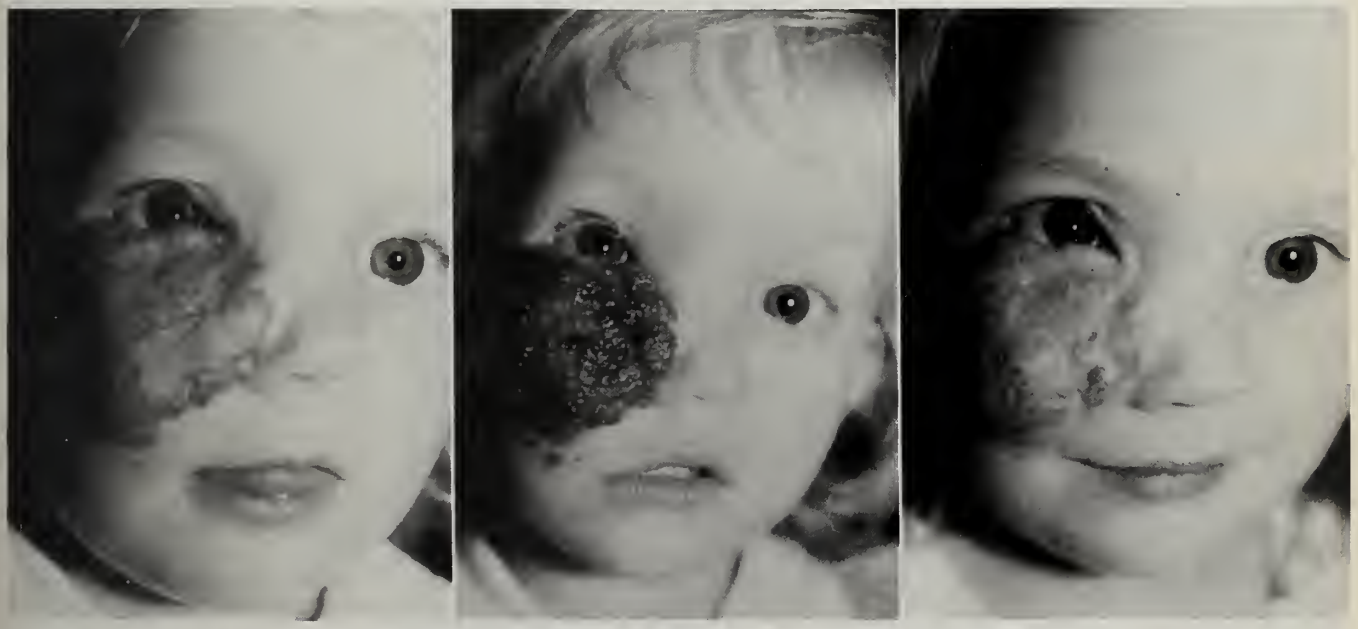

Figure 1.—Case 8: **Left,** Extensive facial hemangioma with some visual field obstruction. **Middle,** Eschar postlaser treatment, which persists from ten days to three weeks. **Right,** Four months postlaser treatment. Note improved visual field.

Figure 2.—Case 11: **Left,** Strawberry hemangioma in a 5½-month-old infant obstructing visual field; before laser treatment. **Middle,** One month postlaser treatment. **Right,** One month postsurgical excision of redundant skin.

lesion interferes with a vital function such as breathing, eating or vision, treatment is indicated. If the lesion impinges on surrounding tissue, becomes ulcerated, infected or bleeds, treatment may also be desirable.[7] Traditional treatments include x-ray, steroids and surgical excision.

Complications of these treatments include damage to surrounding tissues, regrowth of tumor after termination of drug therapy and objectionable scar. All of the above treatments have limited success. In our series, 2 of the 13 patients had prior treatment (systemic steroids for cases 8 and 12).

If a treatment were available that was simple, inexpensive and had very little risk, virtually all of the lesions could be treated, saving the patient and family a great deal of travail.

Our series of 13 cases showed poor to dramatic results

Figure 3.—Case 7: **Left,** Prelaser treatment of lip lesion, which interferes with speech and causes drooling. **Right,** Photo taken at five-month follow-up.

Figure 4.—Case 3: **Left,** This ulcerated inguinal hemangioma was particularly painful, being constantly macerated by urine. **Right,** Photo taken ten months posttreatment.

Figure 5.—Case 6: **Left,** Photo taken before treatment of hemangioma of the arm. **Right,** Six months postlaser treatment.

(Table 1) and only one complication—seizure due to intravascular administration of lidocaine. The lesions in cases 8 (Figure 1) and 11 (Figure 2) decreased in size without aggravation of existing vision problems. In cases 2, 5 and 7 (Figure 3), treatment resulted in reduction of lesions, thereby decreasing problems associated with eating and speech. Case 3 (Figure 4), showing a particularly painful, macerated lesion, was successfully treated with a two-staged laser application. Case 6 (Figure 5) is an example of a fair result, whereas case 13 (Figure 6) shows a poor result. An area in the central portion of the hemangioma is blanched, but the overall size appears to have increased with age.

Cases 1, 3 (Figure 4), 9 (Figure 7) and 11 (Figure 2) all had excellent results from the treatment. It is interesting to note that these lesions are small, ranging in size from 1¼ by 2½ cm to 2½ sq cm, and the largest lesion had the least improvement. We agree with Hobby's observation that lesions treated early may respond better. It would be exciting to treat evolving lesions in the neonatal period. If this became routine, then complicated tumors might be "prevented."

Figure 6.—Case 13: **Left,** A photo of a 3-month-old infant, prelaser treatment, showing a strawberry hemangioma of the nose. **Right,** No response occurred in this case, three months follow-up.

Figure 7.—Case 9: **Left,** A 6-month-old infant with a typical raised strawberry hemangioma of the forehead. **Right,** One-year follow-up with mild skin pigment change noted.

Healing required two to four weeks and was of parental concern in a few cases.

Summary

Strawberry hemangiomas are usually very small to nonexistent at birth. They undergo a rapid increase in size in the first few weeks of life. If they could be treated before attaining significant size, deforming, complicated tumors might be totally prevented.

It is possible that a great deal of patient and family morbidity can be avoided by an inexpensive, uncomplicated outpatient procedure. Argon laser treatment is not definitive treatment in most cases, but seems appropriate palliation for a self-limiting condition. Scarring, the major complication of laser treatments for port-wine stain, has not been seen in any of our cases or the other reported cases.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Bone Marrow Transplantation for Lymphoblastic Leukemia

QUESTION:

Is bone marrow transplantation accepted medical treatment for lymphoblastic leukemia?

If both autologous and donor bone marrow transplantation are accepted medical practice, is one preferred over the other?

OPINION:

In the opinion of the Scientific Advisory Panels on Internal Medicine and Pathology and the Committee on Organ and Tissue Transplantation, allogeneic bone marrow transplantation is considered established medical treatment for selected patients with acute lymphoblastic leukemia who fail to be cured by conventional chemotherapy. For adults younger than 50 years of age during first remission or in second relapse, transplantation using allogeneic bone marrow from a HLA-matched sibling is accepted as effective therapy. However, with recent improvements in the results of chemotherapy, it is uncertain whether transplantation is superior to conventional chemotherapy for patients in first remission. For children in second remission, bone marrow transplantation is definitely the treatment of choice, if a suitable HLA-matched sibling donor is available.

Patients at high risk of recurrence and who lack a HLA-identical donor have received transplants from autologous bone marrow as well as from partially matched donors. The former has been attempted using physical, pharmacological and immunological techniques to deplete marrow of leukemic blood cells. Autologous bone marrow transplantation is currently being used in specialized centers for selected patients in second and subsequent remission who do not have a suitable allogeneic donor and who have no other hopeful alternative when chemotherapy fails. Though preliminary results using autologous bone marrow transplants have been encouraging, the number of patients treated thus far has been small. Further clinical investigation is required to fully determine the long-term efficacy of this treatment before it can be accepted as standard medical practice.

Nonstress Testing in a Physician's Office—A Five-Year Experience

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A study was undertaken to evaluate the use of nonstress testing in a physician's office in the management of high-risk pregnancies. A total of 1,485 office nonstress tests were done on 713 high-risk patients between 32 and 43 weeks' gestation. When indicated the contraction stress test was done in hospital. In all, 485 patients had a nonstress test within a week of their delivery, 97% of which were reactive and 2% were nonreactive. Those fetuses with a nonreactive test result had a significantly increased incidence of abnormal fetal heart rate patterns during labor and intrapartum fetal distress leading to cesarean delivery. With strict adherence to a protocol, nonstress testing in the physician's office can be successful in caring for fetuses thought to be at risk.

(Hill WC, Alderson M, Henderson T: Nonstress testing in a physician's office—A five-year experience. West J Med 1985 Nov; 143:633-635)

Obstetricians are constantly searching for additional methods of antepartum fetal surveillance to evaluate normal and high-risk pregnancies. The tests of antepartum fetal heart rate monitoring are the contraction stress test and the nonstress test. The nonstress test has certain advantages over the contraction stress test in that it requires less time to do, is simpler to interpret and has no contraindications. Various authors have shown that when the nonstress test is done in hospital, it can identify and evaluate a high-risk fetus.[1,2] Outpatient nonstress testing has been investigated by several authors who concluded that it is appropriate for office use.[3,4] Office antepartum fetal heart rate monitoring has increased since it was first introduced in the mid-1970s. There are few reports on the use of the nonstress test in office practice.[4]

We undertook a prospective study in a private practice for five years to evaluate the use of office nonstress testing in managing high-risk pregnancies. The purpose of the study was to test the hypothesis that by strictly adhering to a protocol, the nonstress test can be successful in physicians' offices in monitoring and identifying compromised fetuses. Herein we report our clinical experience with office antepartum fetal heart rate monitoring.

Patients and Methods

A total of 713 high-risk mothers in the private practice of one of us (W.C.H.) underwent 1,485 office nonstress tests for the indications given in Table 1. A number of patients had more than one indication, the most frequent of which was postdate pregnancy. All tests were carried out in an examination room of the office as part of the regular pregnancy evaluation. Only nonstress tests were done. When contraction stress tests were indicated, they were done in hospital. Two nurses and an electrocardiographic technician trained in antepartum fetal heart rate testing did all the nonstress testing. A Corometrics 111A fetal heart rate monitor was used. A tocodynamometer was used to record fetal movement and uterine activity. The fetal heart rate was recorded using the fetal electrocardiogram, ultrasonogram or phonocardiogram.

The tests were done and interpreted with strict adherence to the method and criteria previously described by other investigators.[4-6] When spontaneous fetal activity was not observed or was insufficient, abdominal palpation was used to stimulate the fetus and induce fetal movement. A reactive nonstress test was defined as at least two accelerations of the fetal heart rate during a 10-minute period of at least 15 beats per minute lasting for 15 seconds and repeated within a week in the physician's office. At the end of 40 minutes of observation, if accelerations were insufficient to meet this definition after palpation, the test was considered nonreactive. Those tests that remained sinusoidal or nonreactive for 40 minutes were repeated within 24 hours in the office following a meal. If still nonreactive, the test was followed the same day with a contraction stress test. The average time for doing the nonstress test was 19 ± 5 minutes (mean $\pm$ standard deviation). Estriols were not used in the study group.

In all, 485 fetuses were grouped according to their last

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reactive or nonreactive nonstress test results seven or fewer days before delivery. Intrapartum complications and neonatal outcome in the reactive and nonreactive groups were compared to determine whether these responses accurately identified high-risk fetuses. Perinatal morbidity was defined as a hospital stay longer than five days in the nursery for medical indications. Repetitive, severe, variable or late decelerations during the first stage of labor were considered abnormal fetal heart rate patterns during labor. Intrapartum fetal distress was defined as persistent abnormal fetal heart rate patterns during labor. Statistical comparison of the reactive and nonreactive groups was done using the χ^2 test for unequal expected frequencies.

Results

During the five-year study period, 1,485 nonstress tests were done on 713 high-risk mothers in the physician's office. Distribution of the fetal heart rate patterns during the tests is shown in Table 2. Nonreactive, equivocal and unsatisfactory test results were most common during the first year of the study. Of the 485 fetuses who were delivered within seven days of their last nonstress test, the test results of 469 (97%) were reactive, 10 (2%) were nonreactive and 6 (1%) were equivocal, sinusoidal or unsatisfactory. The perinatal outcome for the nonreactive group was less favorable than for the reactive group, with a significant increase in abnormal fetal heart rate patterns during labor and cesarean sections for intrapartum fetal distress (Table 3). There were no stillbirths of any of the fetuses tested. Two infants died after birth of congenital anomalies.

Thirty nonstress tests remained nonreactive and required a contraction stress test. The latter was not done following ten of these tests, however, due to contraindications or patient refusal. A reactive nonstress test result occurred in six mothers being prepared for their contraction stress testing and no further testing was done. A spontaneous contraction stress test occurred during four nonreactive nonstress tests, the results of three of which were normal and one was abnormal. Ten contraction stress tests were completed in the remaining women with nonreactive nonstress tests as shown in Table 4.

Labor was induced in three mothers who had a positive contraction stress test result. In one of these patients at 43 weeks' gestation, because of meconium-stained amniotic fluid and late decelerations during labor, a cesarean section was done and a male infant with Apgar scores of 5 and 7 at one and five minutes, respectively, was delivered. The second patient at 40 weeks' gestation was suspected of having intrauterine growth retardation. No decelerations occurred during labor and a small-for-gestational-age male infant weighing 2,800 grams with Apgar scores of 6 and 8 was delivered vaginally. The third patient had a spontaneous positive contraction stress test result at 43 weeks' gestation. There was meconium-stained amniotic fluid and variable decelerations during labor. A low forceps delivery for fetal distress was carried out and a female infant with Apgar scores of 5 and 6 was delivered.

Discussion

This report emphasizes the applicability of doing nonstress testing in a physician's office. Nonstress testing done in this manner is accurate. The distribution of fetal heart rate

TABLE 1.—*Indications for the Office Nonstress Test in 713 Patients*

Indications	*Number*	*(%)*
Postdate pregnancy*	335	(42.4)
Suspected growth retardation†	142	(18.0)
Decreased fetal movement‡	130	(16.4)
Preeclampsia	49	(6.2)
Diabetes (all classes)	16	(2.0)
Chronic hypertension	15	(1.9)
Previous stillbirth	11	(1.4)
Miscellaneous	93	(11.8)
Total	791§	

*Pregnancy exceeded 42 weeks.
†Size less than dates by physical examination, ultrasonogram or both.
‡Patient perceived less than usual fetal movement following meals or during the day.
§Some patients had more than one indication.

TABLE 2.—*Distribution of Fetal Heart Rate Patterns During Office Nonstress Testing in 713 Patients*

Heart Rate Patterns	*Tests Number*	*(%)*
Total tests	1,485	
Reactive	1,396	(94.0)
Nonreactive	30	(2.0)
Equivocal	45	(3.0)
Sinusoidal	1	(0.1)
Unsatisfactory	13	(0.9)

TABLE 3.—*Intrapartum Complications and Perinatal Outcome of the Fetuses With Reactive and Nonreactive Test Results**

Complications	*Reactive (N = 496) 97%*	*Nonreactive† (N = 10) 2%*
Neonatal deaths	2 (0.4)‡	0
Perinatal morbidity	32 (6.5)	2 (20)
Abnormal fetal heart rate pattern during labor	18 (3.6)	5 (50)§
Cesarean section for intrapartum fetal distress	4 (0.8)	2 (20)§
Apgar score less than 7 at 1 minute	37 (7.5)	1 (10)
Apgar score less than 7 at 5 minutes	14 (2.8)	1 (10)
Meconium-stained fluid	46 (9.3)	2 (20)

*The last nonstress test was within 7 days of delivery.
†Some infants had more than one complication.
‡The two infants who died had Potter's syndrome.
§Significantly different from the reactive value, $P < .001$.

TABLE 4.—*Persistent Nonreactive Nonstress Test Results*

Test Results	*Number*	*(%)*
Contraction stress test not done	10	(33.3)
Reactivity spontaneously observed	6	(20.0)
Contraction stress test results		
Spontaneous		
Negative	3	(10.0)
Positive	1	(3.3)
Oxytocin-induced		
Negative	6	(20.0)
Equivocal	1	(3.3)
Positive	2	(6.7)
Unsatisfactory	1	(3.3)
Total	30	

responses in Table 2 is what would be expected in a high-risk obstetric practice. Trained personnel in the physician's office can correctly carry out and interpret the nonstress test, but all tests must be reviewed by the physician. The results of office testing are consistent with reports from centers doing hospital-based nonstress tests.[7] Nochimson and co-workers doing the test in two medical centers reported similar results.[8] Using the nonstress test, they were also able to identify high-risk fetuses. Keegan and associates showed that the nonstress test was a practical and accurate outpatient test when used in screening high-risk patients.[3] They suggested the outpatient hospital approach was appropriate for nonstress testing in a physician's office. Our results confirm and expand their findings.

By strictly adhering to a protocol, the nonstress test done in a physician's office can successfully monitor a high-risk fetus and detect an infant who can have an abnormal fetal heart rate pattern during labor. The data in Table 4 show that a nonreactive fetus was identified. The group of fetuses represented in Table 4 had a higher incidence of abnormal fetal heart rate patterns during labor and of cesarean sections for fetal distress. Strict adherence to a protocol is necessary because it will decrease the possibility of misinterpreting or not appropriately following up the test result. Figure 1 provides a protocol for the use of the nonstress test in physicians' offices and shows how it and the contraction stress test can be used together in a complementary manner.[9]

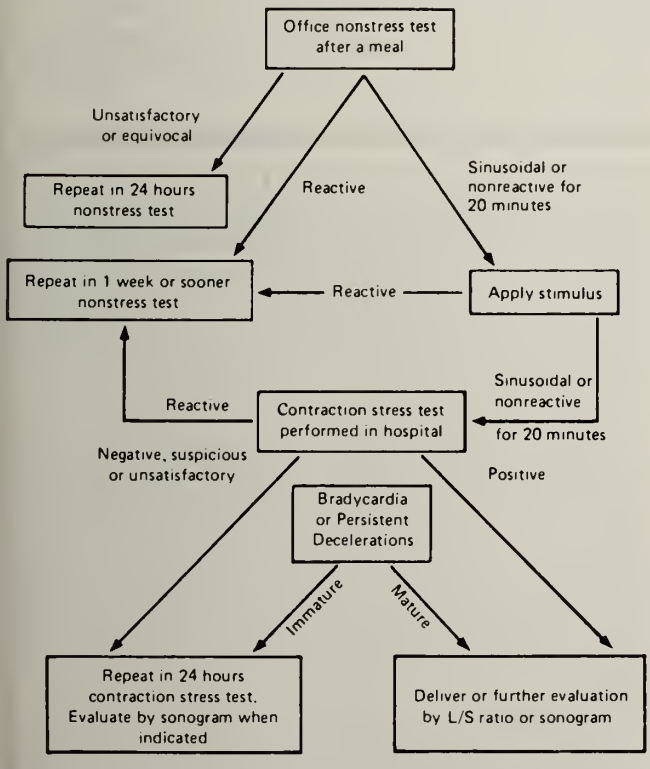
Office nonstress test after a meal
Unsatisfactory or equivocal
Repeat in 24 hours nonstress test
Reactive
Sinusoidal or nonreactive for 20 minutes
Repeat in 1 week or sooner nonstress test
Reactive
Apply stimulus
Sinusoidal or nonreactive for 20 minutes
Reactive
Contraction stress test performed in hospital
Negative, suspicious or unsatisfactory
Positive
Bradycardia or Persistent Decelerations
Immature
Mature
Repeat in 24 hours contraction stress test. Evaluate by sonogram when indicated
Deliver or further evaluation by L/S ratio or sonogram

Figure 1.—A protocol for nonstress testing in a physician's office. L/S = lecithin-sphingomyelin

There are several advantages to using this approach to nonstress testing. The nonstress test done in a physician's office is practical and more convenient for patients than hospital testing because it can be done at the time of the patient's regular appointment. Data from our 1984 survey of physicians doing these tests in their offices show that office nonstress testing is less expensive ($40) than testing done in hospital ($80). The appropriate use of office nonstress testing can decrease the need for hospital-based testing and, in some institutions, overburdening labor and delivery units.

Practical considerations of office nonstress testing include selecting the equipment and reimbursement. Numerous fetal heart rate monitors from at least six companies are now available for private practitioners contemplating office monitoring. Each has certain advantages and disadvantages that should be considered when purchasing a monitor for office use. When selecting an office monitor, some of the features that should be carefully evaluated are cost, method used to process the signal, the printer, paper speed, technique for recording the fetal heart rate and contractions and size of the monitor. Third-party carriers (Medicaid, Blue Cross) reimburse physicians different amounts for doing the office nonstress test but only for specific indications as in Table 1. The average amount reimbursed is $40 (range $33 to $47) based on our recent survey.

In summary, antepartum fetal heart rate monitoring has become a useful office procedure for efficient fetal surveillance by private practitioners.

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Selection of Patients With Non-Small-Cell Lung Carcinoma for Surgical Resection

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Cancer of the lung is rapidly increasing in incidence in both sexes and soon will overtake breast cancer as the most deadly cancer in women. Selection of patients with non-small-cell carcinoma for surgical resection is largely based on preoperative clinical staging, using the American Joint Committee on Cancer's TNM-based group staging protocol. Determining the presence or absence of mediastinal nodal metastasis is paramount and is currently best achieved by computed tomographic scanning of the chest and biopsy of enlarged nodes via mediastinoscopy. Certain types of stage III lesions, previously excluded from surgical treatment, are now recognized as operable.

(Rizk NW: Selection of patients with non-small-cell lung carcinoma for surgical resection [Medical Progress]. West J Med 1985 Nov; 143:636-642)

There is a virtual epidemic of lung cancer in this country. According to estimates published by the American Cancer Society, in 1984 cancer of the lung developed in approximately 139,000 Americans and 121,000 will die of it.[1] Cancer of the lung kills more than twice as many patients as the next most deadly neoplasm, cancer of the colon and rectum. Particularly distressing is the fact that American women are increasingly affected—lung cancer deaths in women have doubled in just the past ten years and this year for the first time will equal deaths from breast cancer. Unfortunately, the potentially curative therapies available for this large group of persons are limited. Combination chemotherapy is used as the primary treatment modality only in the approximately one fifth of lung cancer patients who have the small-cell subtype. For the remainder of patients who have non-small-cell carcinoma, surgical resection remains the only hope for cure at present.

The purposes of this report are to review the following topics: current methods of staging lung cancer, including pertinent information on the route of lymphatic spread of carcinoma of the lung; results of surgical resection in each stage of the disease, and therapy for particular subsets of stage III tumors that are now being treated somewhat differently than they were in the past. The last topic is particularly important because about half of all patients at the time of initial diagnosis will have one of the subsets of stage III disease reviewed here—carcinomas with metastasis to mediastinal nodes, extensive superior sulcus tumors and tumors involving the chest wall. In this review I will not discuss methods of evaluating individual patients to estimate their operative risk and to determine whether they have sufficient pulmonary reserve for lung resection. Likewise, because the therapy for small-cell carcinoma is primarily nonsurgical, it will not be detailed in this report. Interested readers are referred to some of the excellent other sources that cover these subjects.[2-7]

Staging of Lung Cancer

In 1973 the Task Force on the Lung of the American Joint Committee for Cancer Staging and End-Results Reporting (AJC, now the American Joint Committee on Cancer) published a system of rules now generally adhered to for uniform staging.[8] This group devised criteria for applying the TNM (tumor-node-metastasis) system to lung carcinoma. They revised the protocol in 1979 and a manual for staging is available from them upon request (55 E Erie Street, Chicago, IL 60611).

Table 1 defines the TNM categories, according to the AJC. In the tumor (T) categories, a size of less than 3 cm indicates a T_1 lesion, and a size greater than 3 cm signifies a T_2 lesion. Gross extension to neighboring structures, effusion or total lung atelectasis defines T_3 disease. In the nodal (N) categories, spread from the hilar nodes (N_1) to the mediastinal nodes (N_2) is reflected in the staging system. Metastasis, from a practical point of view, is best thought of as either absent (M_0) or present (M_1).

TNM categories of about equal prognosis are grouped by the AJC into stages to assist in devising therapeutic strategies. The stages that correspond to each TNM category are shown

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ABBREVIATIONS USED IN TEXT

AJC = American Joint Committee for Cancer Staging and End-Results Reporting
ATS = American Thoracic Society
CT = computed tomography
TNM = tumor-nodes-metastasis
VASG = Veterans Administration Surgical Group

in Table 2. Disease confined to the lung parenchyma is divided into stage I or II, depending on the size of the primary tumor (T_1 or T_2) and on whether hilar nodal metastasis is absent (N_0) or present (N_1). Tumors extending into extrapulmonary structures (T_3) and those metastatic to mediastinal lymph nodes (N_2) or to extrathoracic sites (M_1) are classified as stage III. Conventionally, stages I and II disease has been treated by surgical resection and stage III by irradiation or chemotherapy.

Methods for determining the TNM status and hence the stage of lung carcinomas are severalfold. The T classification can usually be achieved by conventional chest roentgenography. Computed tomographic (CT) scans of the primary lesion usually offer little additional information and, contrary to an early report,[9] are not extremely helpful in distinguishing benign from malignant nodules.[10]

The M status is determined by a combination of the history and the findings of the physical examination, multiphasic serum screening tests and scans (bone, central nervous system, liver and spleen), if indicated. In low-risk operative candidates, nuclear or CT scans are primarily indicated when the history, physical examination or serum screening test results suggest the possibility of specific extrathoracic organ involvement.[11]

A more vigorous search for extrathoracic metastases by scanning techniques may be justified when a patient is a borderline surgical candidate because of coexisting diseases or extensive nodal involvement. The most sensitive test for bony involvement is a radionuclide bone scan[12]—bone pain usually precedes skeletal radiographic changes but is absent in as many as half of the patients with abnormal radionuclide scans.[12,13]

The lack of specificity of abnormal bone scans in patients without clinical findings of metastasis is a major problem,[14] however, and as much as 90% may have falsely positive results,[15] largely because of osteoarthritis. Nonetheless, in some series, bone scanning is the single most effective radionuclide technique for detecting clinically occult dissemination.[16,17] For liver metastases, CT scanning has superceded radionuclide studies as the most sensitive test. In addition, because spread to the adrenals is relatively common in cases of bronchogenic carcinoma,[18] some clinicians advocate carrying the CT down to the adrenals routinely when the results of other studies are negative.[19] For detecting asymptomatic central nervous system metastases, the yield of CT brain scans is probably in the range of 5%.[20,21] In general, because of the high cost and relatively low yield of all of these scanning techniques, their use should be confined to problematic cases.

The major difficulty in clinical staging resides in determining the N status—the extent of local nodal involvement—before thoracotomy. Lymphatic effluent containing tumor cells from lung tumors drains first to intralobar nodes, then to hilar nodes and finally into mediastinal nodal groups (Figure

TABLE 1.—*American Joint Committee on Cancer's Definitions of T, N and M Categories for Carcinoma of the Lung**

Category	Definition
Primary Tumor (T)	
T_X	Tumor proved by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed, as in the retreatment staging
T_0	No evidence of primary tumor
T_{1S}	Carcinoma in situ
T_1	A tumor that is 3.0 cm or less in greatest diameter, surrounded by lung or visceral pleura and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T_2	A tumor more than 3.0 cm in greatest diameter or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion
T_3	A tumor of any size with direct extension into an adjacent structure such as the parietal pleura or chest wall, the diaphragm or the mediastinum and its contents; or a tumor demonstrable bronchoscopically to involve a main bronchus less than 2.0 cm distal to the carina; or any tumor associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion
Nodal Involvement (N)	
N_0	No demonstrable metastasis to regional lymph nodes
N_1	Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension
N_2	Metastasis to lymph nodes in the mediastinum
Distant Metastasis (M)	
M_X	Not assessed
M_0	No (known) distant metastasis
M_1	Distant metastasis present; specify site(s)

*Adapted from the *Manual for Staging of Cancer*.[8]

TABLE 2.—*American Joint Committee on Cancer's Stage Grouping in Carcinoma of the Lung**

Stage	Description
Occult Carcinoma	
$T_X N_0 M_0$	An occult carcinoma with bronchopulmonary secretions containing malignant cells but without other evidence of the primary tumor or evidence of metastasis to the regional lymph nodes or distant metastasis
Stage I	
$T_{1S} N_0 M_0$	Carcinoma in situ
$T_1 N_0 M_0$ $T_1 N_1 M_0$ $T_2 N_0 M_0$	A tumor that can be classified T_1 without any metastasis or with metastasis to the lymph nodes in the peribronchial or ipsilateral hilar region only, or a tumor that can be classified T_2 without any metastasis to nodes or distant metastasis
Stage II	
$T_2 N_1 M_0$	A tumor classified as T_2 with metastasis to the lymph nodes in the peribronchial or ipsilateral hilar region only
Stage III	
T_3 with any N or M N_2 with any T or M M_1 with any T or N	Any tumor more extensive than T_2, or any tumor with metastasis to the lymph nodes in the mediastinum, or any tumor with distant metastasis

T = tumor; N = node; M = metastasis

*Adapted from the *Manual for Staging of Cancer*.[8]

1). The presence of metastases within mediastinal nodes has been the most common cause for excluding patients from attempts at surgical resection. Although this exclusion is now being reevaluated to some degree, determining the presence or absence of nodal metastasis is essential for deciding on appropriate therapy.

Conventional imaging techniques used to assess the hila and mediastinum for metastases include tomography and 55-degree oblique radiographic views. Gallium scanning has sometimes also proved useful; if the primary tumor concentrates gallium, approximately 80% of cases of nodal metastasis will also concentrate the isotope and hence be detected.[23] More recently, clinicians have used CT scanning of the chest to search for mediastinal nodal metastases. With this very sensitive technique, even mediastinal nodes of normal size can frequently be seen. In one large series, lymph nodes could be identified in 88% of normal volunteers by chest CT and averaged 5.5 ± 2.8 mm in size.[24] In patients with lung cancer, nodal sizes much larger than this usually reflect the presence of malignant metastasis.

A fundamental problem, however, with using conventional roentgenographic and chest CT imaging techniques for staging is the lack of specificity of lymph node enlargement. Normal-sized nodes can contain tumor and large nodes may be reactive and benign. False-positive CT scans (nodal enlargement without nodal metastasis) are particularly serious because patients could be inappropriately excluded from potentially curative operations because of them. In the most alarming of the reported series, of 17 patients with lung cancer and mediastinal nodes greater than 1 cm in size, only two had intranodal tumor.[25] Other investigators have reported false-positive rates of 4% to 37%.[26-28] One group attempted to circumvent these false-positive results by using the larger nodal size of 1½ cm as the criterion for separating benignity from malignancy.[29] This approach reduces the false-positive rate but, in my view, should not substitute for biopsy and histopathologic examination of enlarged mediastinal lymph nodes, since incorrectly excluding a patient from operation on the basis of imaging techniques, even occasionally, must be viewed as a serious and assuredly fatal error.

A related but separate issue is whether patients with CT scans of the chest that fail to show enlarged nodes can be spared preoperative lymph node biopsies via mediastinoscopy. With the newer scanners, preliminary evidence is accruing that the false-negative rate (normal-sized nodes with nodal metastasis) is sufficiently low, in the range of 5%, that thoracotomies can be done without fear of undetected nodal metastases in the vast majority of cases.[26-28] Use of this strategy, however, presupposes that the best published results can be reproduced in other institutions where CT interpretation may not be as expert.

When nodal biopsy is indicated, it can be done by conventional mediastinoscopy or by the newer technique of bronchoscopic needle aspiration. In the latter procedure, lymph nodes adjacent to the central airways are punctured transbronchially by a small-bore needle inserted through the bronchoscope at the time of diagnostic bronchoscopy.[30] Complications are few and the yield of positive aspirates is relatively high.[30,31] The false-negative rate, however, is not established, and the technique provides no opportunity for visually inspecting the lymph nodes. For these reasons most patients should undergo the more definitive mediastinoscopy.

Two types of mediastinoscopy can be done. Standard cervical mediastinoscopy is carried out under general anesthesia via a transverse incision above the suprasternal notch. A modified laryngoscope is advanced in the pretracheal fascia down to the carina by blunt dissection. Paratracheal nodes and, to a lesser degree, anterior subcarinal nodes are accessible for biopsy by this approach. The dissection does not expose the anterior preaortic or subaortic nodes, but a biopsy can be done of these by anterior mediastinoscopy, a separate procedure that requires an incision in the left second intercostal space.[32]

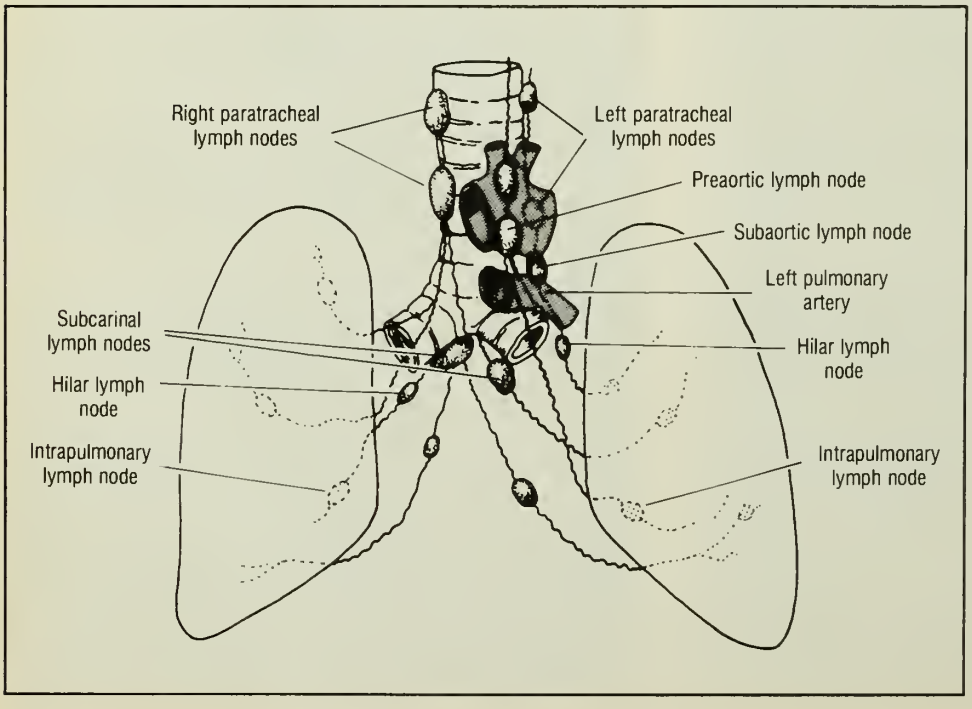

Figure 1.—Lymphatic drainage of the lung, depicting the pathways of lymphatic spread of lung carcinoma and the anatomic locations of nodal groups (adapted from Hashim et al[22]).

Cervical mediastinoscopy is widely available, but anterior mediastinoscopy is less widely practiced, many surgeons preferring to do a "mini-thoracotomy" to sample the preaortic and subaortic nodal groups.

Until recently, the decision about which type of mediastinoscopy to do had been based primarily on the site of the primary tumor, since the patterns of spread of lung carcinoma have been well known for many years (Figure 2). With the advent of chest CT scanning to search for nodal enlargement, the most productive procedure can now be selected on the basis of the specific CT findings in each case. With the use of a combined approach of CT imaging and mediastinoscopy to sample accessible enlarged nodes, gross but unsuspected disease that precludes resection should only infrequently be discovered at thoracotomy. However, because of microscopic metastatic disease obvious only to a pathologist's histologic examination, a small percentage of the time the postsurgical staging will reflect more advanced disease than anticipated clinically.

Results of Surgical Resection

The TNM system and stage grouping for carcinoma of the lung, as devised by the AJC and presented above, were based on a retrospective review of more than 2,000 cases of resected lung cancer and were designed to stratify the available survival data.[8] The AJC has published the resulting survival curves for their patients for the major histologic subtypes (Figure 3). Small-cell carcinomas were excluded from analysis because few were resected; the dismal operative cure rate had already been recognized at the time of this work. The appreciable differences between the presurgical and postsurgical staging survival curves to some degree reflect the inadequacy of preoperative staging techniques in their patients—this situation may well have improved in the years since the AJC system was devised, due to availability of CT scanning of the chest and directed biopsy procedures.

Data from other large surgical series clearly show the validity of the AJC's staging system for predicting the outcome of surgical resection. For example, in 1973 the Veterans Administration Surgical Group (VASG) reported results in more than 2,341 patients showing that the presence or absence of nodal metastasis was the most important determinant of survival.[34] Overall five-year survival for patients with negative nodes (N_0), as determined by life-table methods, was 33.7% in the VASG studies. Patients with hilar nodal involvement (N_1) had a 17.4% five-year survival rate, compared with 8.9% survival for patients with involved mediastinal nodes. (N_2). Slightly better outcomes were achieved in a large series from the University of Michigan. Patients with hilar metastasis (N_1) had a 31% five-year survival, compared with a 23% rate for those with mediastinal metastasis (N_2) who underwent radiation therapy.[35] These results, like those studies by the AJC, were influenced by cell type. Other Veterans Administration and Armed Forces trials have validated the importance of the size of the tumor (T notation) in predicting survival, showing an approximately 50% better five-year survival in patients with tumors smaller than 3.5 cm.[36] Many other surgical series confirm the validity of the major stratifiers in the AJC classification scheme.

Therapy for Particular Subsets of Stage III Disease

Although the broad outline of the AJC staging scheme has been amply confirmed in the past decade, there is currently substantial debate about the uniformity of prognosis in patients with stage III tumors because there are now several studies showing surprisingly good surgical results in a small number of carefully selected patients.[37-39] These reports have spurred efforts to determine which patients with stage III disease might be amenable to operation and hence be rescued from the dismal prognosis of the group as a whole. Special interest has focused on patients with metastases in mediastinal nodes, those with extensive superior sulcus tumors and patients with tumors involving the chest wall.

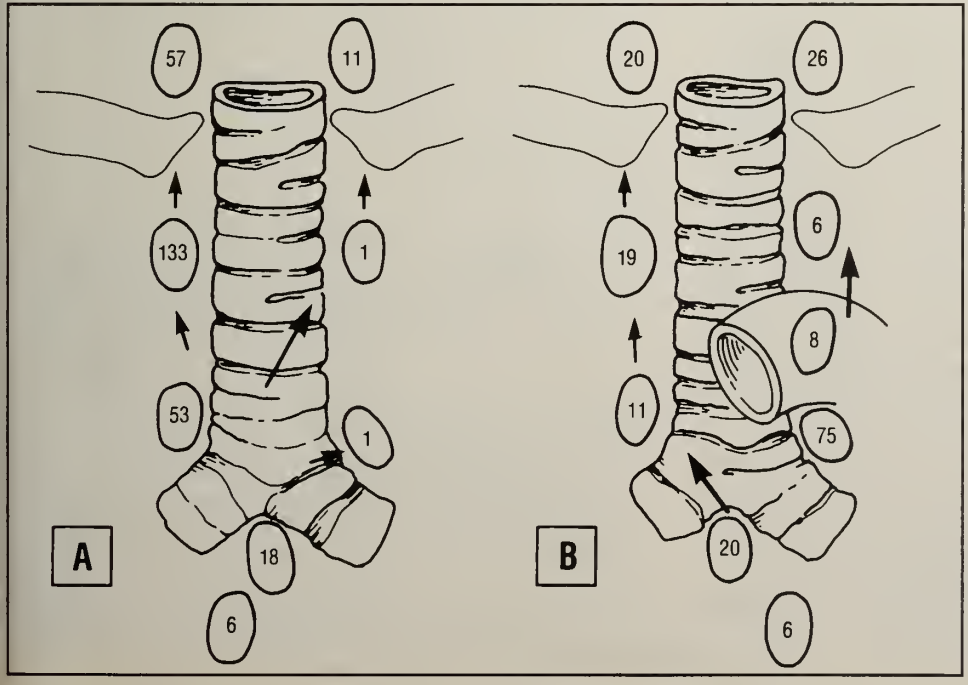

Figure 2.—A, Site and number of lymph node metastases in 423 cases of right lung carcinoma. Most of the metastases were ipsilateral. **B**, Site and number of lymph node metastases in 326 cases of left lung carcinoma. Note the bilateral spread and frequent subaortic nodal disease (adapted from Nohl-Oser[33]).

Carcinomas Metastatic to Mediastinal Nodes

Operations for patients with resectable primary tumors and metastasis to mediastinal nodes have been particularly controversial. A consensus is emerging that at least some of these patients could benefit from operation; the task at hand is to determine which of the patients should have resection. At least two important determinants of postsurgical outcome have been recognized. The first is the integrity of the capsule of the involved lymph nodes because Larsson clearly showed that patients with metastatic tumor completely confined within the capsule of mediastinal lymph nodes ("intranodal disease") have a much better prognosis than patients with tumors growing through the capsule ("perinodal disease").[40] A second but more controversial determinant of surgical outcome may well be the histologic type of the tumor. An autopsy series of patients dying unexpectedly after resections for lung cancer showed that those patients who had unsuspected residual squamous cell carcinoma tended to have incompletely resected intrathoracic tumor.[41] Patients with adenocarcinoma who had residual disease were more likely to have extrathoracic metastasis. These data suggest that better results, particularly in cases of squamous cell carcinoma, might be achieved with more intensive therapy confined to the thorax. Recently more extensive surgical approaches, including radical mediastinal lymph node resections, have been done in an attempt to remove intranodal tumor that has spread to the mediastinum. Many of these patients have also been given adjuvant mediastinal radiation therapy, and prospec-

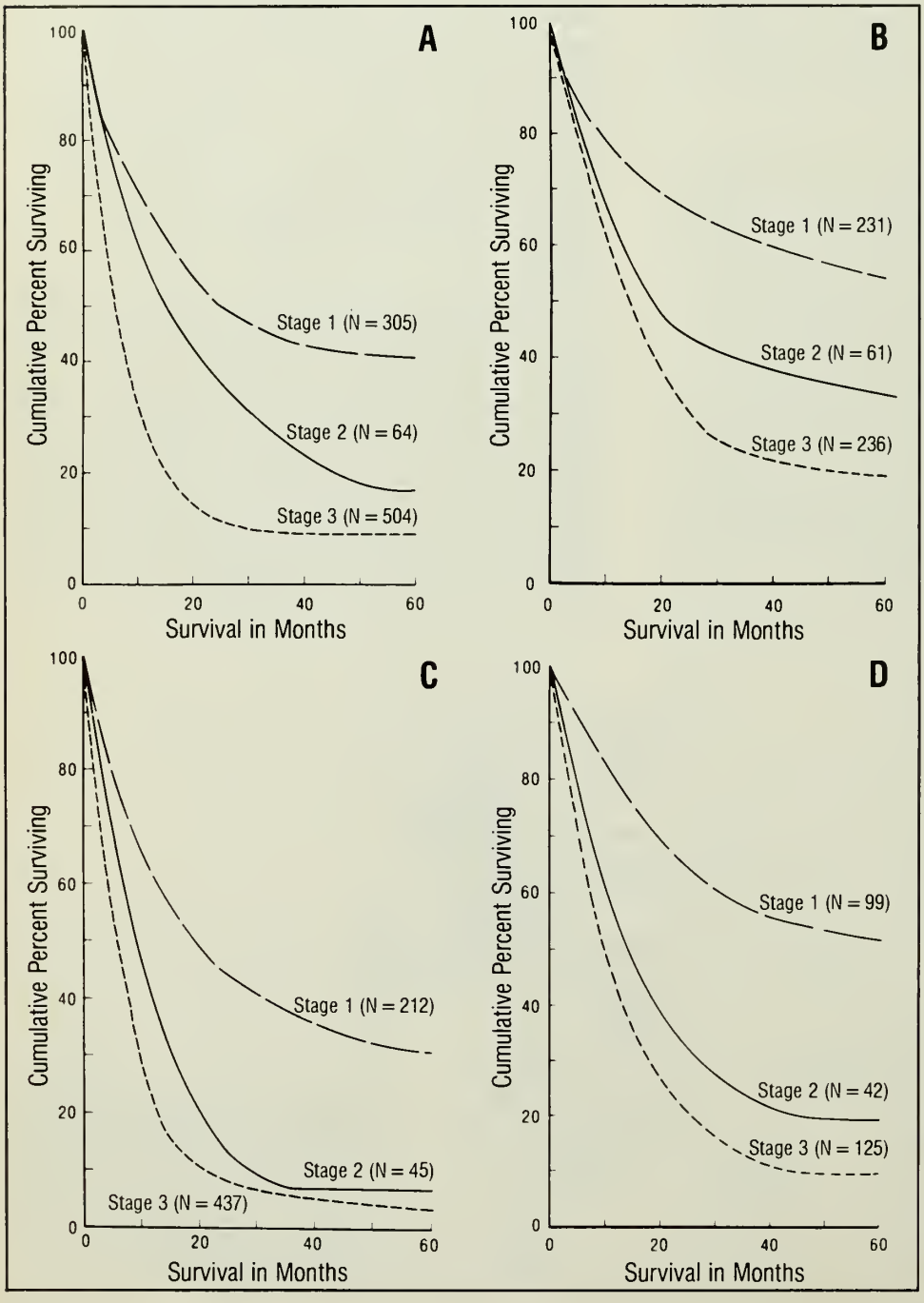

Figure 3.—Survival curves published by the American Joint Committee for Cancer Staging and End-Results Reporting for patients with lung carcinoma, according to clinical or pathologic stage and cell type. **A,** Survival of patients with squamous cell carcinoma of lung by clinical diagnostic stage. **B,** Survival of patients with squamous cell carcinoma by postsurgical pathologic stage. **C,** Survival of patients with adenocarcinoma and undifferentiated large cell carcinoma of lung by clinical diagnostic stage. **D,** Survival of patients with adenocarcinoma and undifferentiated large cell carcinoma by postsurgical pathologic stage (reproduced with permission from the American Joint Committee on Cancer[8]).

tive trials assessing the value of postoperative irradiation in this setting are now ongoing.

Pearson and co-workers recently reviewed the results of these surgical resections in patients with N_2 disease in the 12 reports published up to 1982, adding an additional 141 cases.[39] Patients with N_2 disease who underwent resection without adjuvant irradiation or chemotherapy had five-year survival rates ranging from 0% to 29%. Results in patients having an operation and adjuvant therapy were somewhat better, varying from 19% to 30%. In some but not all of the reports, patients with squamous cell carcinoma lived longer than did patients with adenocarcinoma or large-cell tumors. This review also stressed that patients with N_2 disease and normal results on mediastinoscopy and whose N_2 status is discovered at the surgical procedure have a better prognosis than those with abnormal findings on mediastinoscopy; presumably this reflects a smaller tumor burden (more exclusively intranodal disease) in the mediastinoscopy-negative group.

A major problem in reviewing these series is the inadequate characterization of the anatomic location of the involved mediastinal nodes in each patient. Because there may well be important prognostic implications of the exact site of nodal involvement, the patient groups reported in these series may not be strictly comparable. This may account for the differences among reported postsurgical survival in patients having N_2 disease. To address this problem, a committee of the American Thoracic Society (ATS) has recently devised and published a detailed mediastinal lymph node map that precisely defines the anatomy of regional lymph nodes and relates it to CT images.[42] By lymph node "mapping," they are attempting to divide patients with N_2 disease into subgroups with different prognoses depending on the exact nodal groups involved. This will be done prospectively with both CT scanning and intraoperative staging biopsies, and the ATS is urging all reporting groups to adhere to the standard map.

A substantial risk of the new enthusiasm for operating on more patients with N_2 disease is that it may be applied indiscriminately without adequate preoperative staging. As Pearson and associates pointed out, reports from two aggressive surgical groups, those of Martini and Naruke and colleagues,[37,38] show a complete resectability rate of less than 60% out of a total of 705 thoracotomies. Significantly, these patients had limited preoperative staging. Although many of the patients underwent incomplete resection or had intraoperative radiation implants, this may not be the case in other centers that adopt limited preoperative staging protocols. It must be borne in mind, as Martini and co-workers pointed out, that only about 10% of all patients with N_2 lesions and non-small-cell carcinoma will have tumor that is completely resectable.[43]

Clearly, restrictive criteria must be applied to avoid a huge excess of unnecessary thoracotomies in patients with N_2 disease. Published results from carefully selected and sometimes postsurgically determined subgroups of N_2 disease must not be confused with possible results in the overall group of persons with N_2 disease. More data, obtained by investigators adhering to the new ATS lymph node map, are clearly essential before firm recommendations for surgical resection can be issued. For the time being, a reasonable approach to N_2 lesions is to consider operation for resectable primary tumors, particularly of the squamous cell type, associated with ipsilateral intranodal mediastinal metastases only.

Superior Sulcus Tumors

In 1932 Pancoast described a constellation of clinical findings found in tumors located at the superior sulcus of the lung.[44] These tumors are now commonly termed either superior sulcus or Pancoast's tumors. He wrote that they were "characterized clinically by pain around the shoulder and down the arm, Horner's syndrome and atrophy of the muscles of the hand" with "always more or less local rib destruction and often vertebral infiltration."[44] The signs and symptoms of tumors in this area commonly relate to local invasion of the stellate ganglion, the lower trunk of the brachial plexus, vertebral bodies or upper ribs. Although originally singled out because of their distinctive clinical findings, in the past 20 years these tumors have been considered a special type of lung cancer because of their surprisingly favorable response to radical therapy.

Before the current treatment modalities, these locally invasive (T_3) tumors were uniformly fatal, with an average survival of about a year. The first promising results, obtained using combined preoperative irradiation and extended resections, were reported by Shaw and associates in 1961[45]; subsequently Paulson's group at Baylor reported a 35% five-year actuarial survival.[46] Although not all authors have been so successful, several additional groups have now published results comparable to those of Paulson.[47-49] Patients with hilar or mediastinal nodal involvement have uniformly done very poorly. Nearly all of the salvage has been in patients with locally invasive disease without lymphatic spread. To assess this adequately, Paulson and others have recommended the use of mediastinoscopy and CT scanning of the mediastinum. Without routine use of these preoperative staging techniques, as many as half of the thoracotomies may be in vain. Certainly the major risk of this extensive therapy is the high operative and perioperative mortality.

Tumors Invading the Chest Wall

The principles learned from treating superior sulcus tumors seem to apply equally well to those tumors invading the chest wall. Two reports from the 1960s showed the feasibility of en bloc resections of tumors arising in the lung and invading the thoracic cage and showed moderately good five-year survival rates.[50,51] Although patients in these early series were not staged by current AJC criteria, only 9 of the 60 reported were said to have had positive "hilar nodes." A more recent study from the Mayo Clinic, using AJC staging methods, clearly shows the significance of nodal involvement in determining prognosis.[52] Actuarial five-year survival for patients who survived operation with $T_3N_0M_0$ neoplasms was 53.7%; this compared with a 7.4% survival rate for patients with $T_3N_1M_0$ and $T_3N_2M_0$ lesions.

Although reconstruction of the chest wall in these operations can be achieved with Marlex mesh or by using autogenous chest wall or scapular musculature, these extensive procedures clearly can result in many deaths. For example, the operative mortality in the 66 patients at the Mayo Clinic (Rochester, Minn) was 15.2%.[52] Martini's group at Memorial Sloan-Kettering (New York) claims that high mortality rates can be avoided by the use of rigid prostheses to repair chest wall defects and by plastic surgical assistance in

cutaneous reconstruction.[49] They report only two deaths in 87 cases. Such large discrepancies in operative mortality suggest that variations in the technical aspects of the operation are extremely important determinants of outcome.

Summary

Cancer of the lung is the most common cause of cancer death in the United States and is rapidly increasing. All patients with this disorder should be classified in accordance with the AJC's TNM and group staging protocols. The most critical factor in determining the resectability of a patient's tumor is the extent of nodal metastasis. Chest CT scanning with mediastinoscopy directed towards accessible enlarged nodes is probably the best current method to assess nodal status. Patients with stages I and II disease and non-small-cell carcinoma are best treated with definitive surgical resection. There are data to suggest that patients with stage III disease characterized by ipsilateral intranodal mediastinal metastases may benefit from resection of the primary lesion and the involved mediastinal nodes. Postoperative mediastinal irradiation is probably warranted in this circumstance. Patients with superior sulcus tumors that have not metastasized systemically or spread to mediastinal lymph nodes should undergo preoperative irradiation and en bloc resection. Tumors that have invaded the chest wall but have not metastasized systemically or to mediastinal lymph nodes are also amenable to en bloc resection. The perioperative mortality of en bloc resection for both superior sulcus and chest wall tumors will be high unless done by expert thoracic surgical groups experienced with reconstructive techniques.

Due to widely varying reported surgical outcomes in patients with N_2 disease, more precise data are urgently needed. Investigators should adhere to the newly published ATS lymph node map, so that further prognostic determinants of outcomes in stage III disease can be identified.

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Specialty Conference

Thyroid Disease in the Elderly—Missed Diagnosis or Overdiagnosis?

Discussants, MARK J. ROSENTHAL, MD, *and* CLARE JEANNE SANCHEZ, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

MARK J. ROSENTHAL, MD:* Thyroid disease, especially hypothyroidism, is common among the elderly. Because the presenting illness is usually atypical, thyroid screening is advisable. The following case and discussion show the pitfalls of thyroid function interpretation, including falsely low and high thyroxine levels.

Report of a Case

CLARE JEANNE SANCHEZ, MD:† The patient, a 77-year-old man, presented with lethargy and weight loss. His brother had noted generalized deterioration for several months, manifested by decreased memory, poor appetite and increasing weakness. The patient ate only sausage for breakfast, sweet rolls the rest of the day and claimed to have lost 18 kg (40 lb) during this period. He had also fainted several times over the past six months, with nothing to suggest head trauma, seizure activity or myocardial infarction. There was no history of a cardiac murmur, arrhythmias, night sweats, fever or chills. The patient did complain of dyspnea and weakness while walking short distances. He was incontinent of urine and occasionally incontinent of stool.

The medical history was significant for hypertension, a transurethral prostatectomy for benign prostatic hypertrophy, a collapsed lung of uncertain cause five years before admission and removal of bilateral cataracts. The patient is a retired farmer and mechanic who has never married and is basically a "loner." He said he did not abuse alcohol and that he had quit smoking years ago.

Important physical findings were as follows: He was cachectic and disheveled but in no acute distress. He was alert and cooperative, with appropriate affect, but oriented only to person and place. Remote memory was intact; however, he remembered only one of three objects at three minutes. Supine, his blood pressure was 150/100 mm of mercury and his pulse rate was 88 beats per minute. While standing, his blood pressure fell to 120/80 mm of mercury and his pulse rate was 112.

On head and neck examination he had only iridectomies and grade II hypertensive retinopathy. The thyroid was palpably normal. There was pronounced muscle wasting of the neck, thorax and proximal extremities. The lungs were clear. On cardiac examination there was a sustained, 3 cm in diameter, left ventricular impulse in the fifth intercostal space at the midclavicular line and a grade 3/6 apical systolic ejection murmur that radiated into the aortic area and both carotids. The abdomen was scaphoid without masses. Rectal tone was poor, with brown stool that was Hemoccult-negative.

On neurologic examination he had intact sensations of light touch, vibration and pinprick. Muscle strength was 4+/5+. No pathologic reflexes were noted and deep tendon reflexes were symmetric.

Laboratory studies disclosed a hematocrit of 39% with normal indices, a serum albumin level of 3.6 grams per dl, Westergren sedimentation rate of 90 mm per hour, a folate level of less than 1 μg per dl and skin test anergy to purified-protein derivative and streptokinase-streptodornase. Results of routine laboratory studies were otherwise normal except for thyroid function tests. A serum thyroxine (T_4) level was 5.7 μg per dl (normal, 4.5 to 11.5); triiodothyronine (T_3) resin uptake was 40.1 relative % (normal, 35 to 45); total T_3, 60 μg per dl (normal, 72 to 210), and thyroid-stimulating hormone (TSH) was 9.2 μU per ml (normal <5).

Hospital Course

The patient was admitted to the general medical service, where initial workup for dementia elicited the thyroid values reported, and a regimen of levothyroxine sodium (Synthroid), 0.025 mg, was begun. He was then transferred to the Geriatric Evaluation Unit for further workup of his mental state, syncope and urinary incontinence and for nutritional support. The patient was found to be folate-deficient and therapy was begun. Echocardiographic evaluation of his syncope sug-

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ABBREVIATIONS USED IN TEXT

rT_3 = reverse triiodothyronine
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

gested aortic stenosis. The patient's mental state improved dramatically within a week of transfer, such that he was alert and oriented. A cardiac surgical procedure was then considered, and catheterization showed significant aortic stenosis and two-vessel coronary disease. On 24-hour Holter monitoring he had supraventricular tachyarrhythmias, for which digitalis therapy was begun. Formal neuropsychiatric testing was done, findings of which validated that the patient was able to make appropriate decisions. The cardiac surgical team was then willing to consider aortic valve replacement, but the patient refused an operation.

With appropriate nutritional supplementation from dietary service, the patient had gained 4 kg (9 lb) by discharge. Evaluation of the urinary incontinence showed urinary retention that resolved spontaneously. Cystoscopy and an intravenous pyelogram were normal. The patient was treated for an enterococcus urinary tract infection.

On leaving the hospital for a boarding home, he was receiving digoxin and levothyroxine. Visiting nurse services and cardiology clinic follow-up were arranged. The patient's condition at discharge was considerably improved, and he is reportedly doing very well at this time, has moved into a board-and-care facility and hopes to move back into his own home soon.

Discussion

DR ROSENTHAL: This case exemplifies how difficult geriatric medicine can be. The patient's main problems on admission were mental deterioration with incontinence, weight loss with anorexia and falling with syncope. These are common problems in the elderly. I will use a discussion of this case as a framework to review an approach to geriatric medicine in general and thyroid dysfunction in particular.

Very often, as happened for this patient, the clues to disease in the elderly are subtle and misleading. By necessity, we turn to laboratory studies. Yet, even with the laboratory results as presented here, I am unsure what were the actual contributors to this patient's illness. Despite that uncertainty, the patient's condition improved and he returned to his normal life-style. Because disease among the elderly is usually chronic and incurable, rather than fixing on diagnostic labels, a more beneficial focus aims to minimize the disability caused by illness.

Diseases go unrecognized in those older than 75 years because of confounding factors: disease presentation is atypical; the nonspecificity of signs and symptoms masks underlying disease, and the elderly, like this patient, are often burdened by not one, but several, disease states, interactions among which further obscure the clinical picture.

Disease states often appear different in an older than in a younger patient population. For example, the elderly more often have silent myocardial infarction and afebrile bacteremia.[1] Thyroid disease also presents atypically. Older patients who have thyrotoxicosis are apathetic, depressed and anorectic, not—as in younger patients—agitated, with a voracious appetite. The usual hyperadrenergic signs of hyperthyroidism, such as tachycardia and lid lag, are frequently absent,[2] perhaps due to an age-related defect in catecholamine receptor-adenylate cyclase coupling.[3]

Hypothyroidism, too, presents atypically in elderly persons. Of 46 cases reviewed by Bahemuka and Hodkinson, less than a third showed typical signs and symptoms.[4] Hypothyroidism, which is very common among the elderly, is in many respects the great masquerader of geriatrics. Not only are its manifestations atypical in the elderly, but a nonspecific clinical picture is particularly common.

Nonspecific Presentations of Hypothyroidism

Elderly patients tend to present with a limited number of nonspecific syndromes: failure to thrive, mental confusion, weight loss with poor appetite, falling episodes, incontinence and depression. Remarkably, this patient had every one of these problems on admission, all of which can be explained by hypothyroidism.

Yet, hypothyroidism often goes unrecognized until an advanced state, in part because of a superficial resemblance to aging itself. Both conditions are associated with such symptoms as dry skin, constipation and depression as well as an increased incidence of atherosclerosis, hyperlipidemia and altered catecholamine physiology. Because of these similarities, it has been proposed that decreased thyroid activity actually leads to aging and, indeed, some evidence supports the presence of a postpubertal pituitary factor in rodents that interferes with the peripheral actions of thyroid hormones.[5]

Table 1 lists some of the reported presentations of hypothyroidism, many of which are nonspecific. Most common is diminishing mobility and deteriorating general health. Because of poor appetite, weight loss is actually more frequent than weight gain. Recurrent falls are caused by poor mobility, weakness or neurologic disease.

Rheumatic complaints are common among elderly persons with hypothyroidism.[6,7] Aches and arthralgias are reminiscent of polymyalgia rheumatica. Muscle leak of creatine kinase combined with weakness mimics polymyositis,[8] whereas stiffness can be confused with parkinsonism. The incidence of pseudogout is increased, with acute attacks occurring most often after the initiation of thyroxine therapy.[9]

In rare cases, noninflammatory but highly viscous joint effusions develop. In patients with long-standing disease, such exudative effusions can appear almost anywhere—pleura, pericardium, peritoneum and even in the eyes, ears and testes.[10] These generally clear with hormonal replacement and are apparently due to altered capillary membrane permeability. Metabolic complications also ensue. The elderly, in general, have an increased tendency to antidiuretic

TABLE 1.—*Confusing Presentations of Hypothyroidism in the Elderly*

Failure to thrive	Neurologic
Weight loss	Psychosis/myxedema madness
Falls	Dementia
"Rheumatism"/weakness	Depression
Exudative effusions	Coma
Ileus	Seizures/drop attacks
Anemia	Deafness
Hyponatremia	Ataxia
	Carpal tunnel syndrome

hormone-related hyponatremia,[11] which is worsened by thyroid deficiency.[12] Constipation is another common problem for hypothyroid patients, but more serious gastrointestinal presentations include ileus and megacolon. Because surgical procedures are extremely hazardous in such patients, making a diagnosis is critical.

About half of hypothyroid patients have mild anemia; the hemoglobin is usually about 9 grams per dl.[13] The picture resembles anemia of chronic disease and may be due to a decreased tissue demand for oxygen in the hypothyroid state. Such anemia tends to correct after 3 to 12 months of thyroxine therapy. Mild macrocytosis is the most common hematologic abnormality because the mean corpuscular volume falls in nearly all treated patients. In hypothyroid elderly patients with pronounced anemia, other diagnoses should be considered. Pernicious anemia occurs in 10% of those with autoimmune thyroid disease, and folate deficiency has been reported in 20% of hypothyroid patients.[14] Subnormal folate absorption may be due to myxedematous bowel, but the significance of low folate levels is not altogether clear, since a number of the reported patients had neither anemia nor macrocytosis.

Does Hypothyroidism Cause Dementia?

Neurologic complications of hypothyroidism are commonly debilitating.[15] All hypothyroid patients tend to be lethargic, but bradyphrenia—that is, substantial psychomotor retardation—can be confused with dementia. For example, a patient I saw in clinic reportedly could not answer where or who she was and appeared totally confused. When allowed long enough time to answer, her responses were coherent though hoarse.

True organic psychoses develop with chronic hypothyroidism. In 1949, Ascher coined the term myxedema madness to describe such patients.[16] Interestingly, his diagnosis of myxedema was based on comparing photographs before and after thyroid hormone treatment. In two studies from the late 1950s, 3% to 5% of hypothyroid patients were psychotic, presenting often with agitated paranoia and auditory hallucinations.[15] Of Asher's initial group of 14 patients, 9 were cured and 2 improved partially. Those odds are considerably better than for patients who are demented and hypothyroid, such patients being predominantly elderly.

Whether hypothyroidism is incidental to or causes dementia is difficult to answer. Almost all hypothyroid patients have mild cognitive deficits: poor recent memory, difficulty concentrating and inattention.[17] Yet the incidence of hypothyroidism in a demented population seems to be the same as in the general population. In one study of 53 demented patients older than 65 years, 1 person with hypothyroidism did not improve with therapy.[18] In another study, 4 of 107 demented patients were hypothyroid, only 1 of whom improved.[19] Of 70 demented patients I have screened, 6 clearly had hypothyroidism, but only the patient presented here, who was probably not hypothyroid, improved. Anecdotal experience suggests that if patients are diagnosed and treated early, their dementia is reversible.[20] In most cases, I suspect that cognition will improve little with thyroxine replacement, though patients may function better.

Depression sometimes presents as cognitive defects, termed pseudodementia, that can be confused with hypothyroid dementia. Depression, already common in the elderly, can be worsened or promoted by hypothyroidism and responds well to replacement therapy. Such patients have hypothyroid apathy and lethargy and are often, in addition, irritable and nervous, with outbreaks of temper.

Myxedema coma is the most feared neurologic complication of hypothyroidism.[21] Though rare, like dementia it affects primarily the elderly, in whom coma is precipitated by factors such as stroke, sedation or infection. Hyponatremia and hypothermia are nonspecific clues. Seizures can herald the onset of coma. The prognosis is poor; mortality is still nearly 50%.

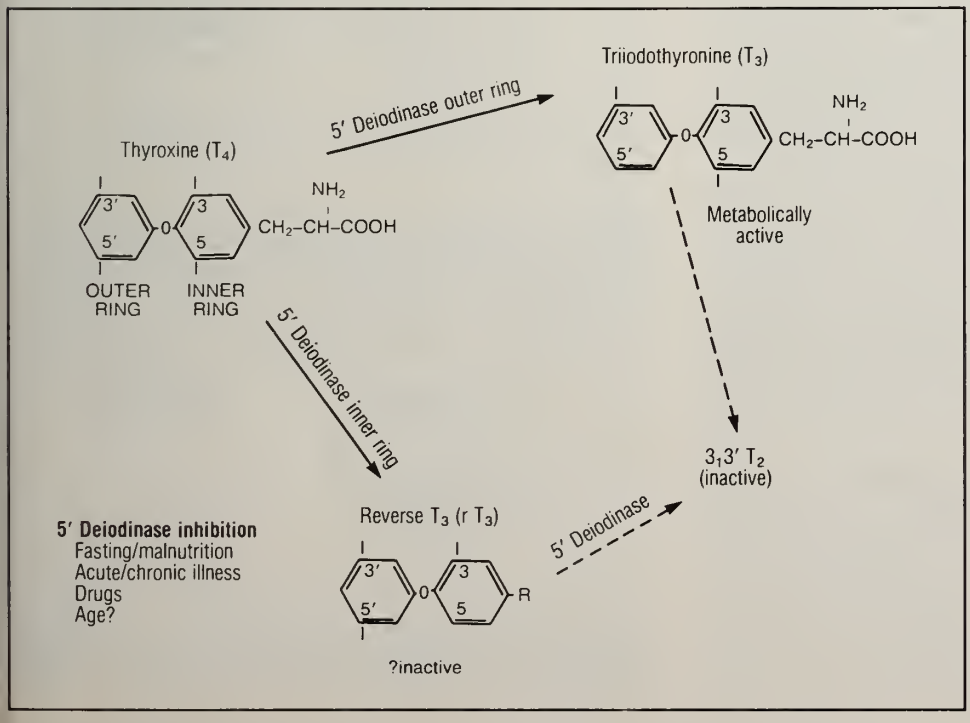

Figure 1.—The diagram shows metabolic patterns that contribute to low triiodothyronine syndrome.

Hypothyroidism: Diagnosis or Overdiagnosis?

Not only is hypothyroidism insidious and misleading but it is common among the elderly. The overall prevalence in this group is 2% to 5%.[4,22-24] Screening studies among in-hospital patients not previously suspected of having thyroid disease found 2.4% with overtly low T_4 levels.[4,23] A recent report suggests that patients with increased TSH values despite T_4 levels within the normal range benefit from replacement therapy.[25] In one study, fully 24% of healthy people older than 60 years had elevated TSH levels.[24] Given such a high prevalence of occult thyroid disease and the frequency of atypical, nonspecific presentations, I believe that screening thyroid tests are useful even in a healthy elderly population and definitely indicated in ailing elderly persons.

Yet many ailments affect thyroid homeostasis, leading to confusion in interpreting thyroid tests. Triiodothyronine is the primary active form of thyroid hormone, produced mostly by monodeiodination of T_4 after release from the thyroid gland (Figure 1). The activity of 5′-deiodinase, the enzyme that generates T_3 by removing an iodine from the outer ring of T_4, is inhibited by a wide variety of insults, including starvation, acute or chronic illness and drugs. Aging, too, has been reported to decrease T_3 levels. Because not all studies show this, I presume that low T_3 levels in the elderly are related to illness, poor diet or other concomitants of aging rather than to aging per se.[26] There is a second enzyme that removes iodine from the inner ring of T_4, the activity of which is not affected by the processes listed above. Removing this iodine yields reverse T_3 (rT_3). Though the function of rT_3 is unknown, it accumulates with decreased outer ring deiodination.

Collectively, this change in thyroid hormone processing, decreased T_3 and increased rT_3, is termed "euthyroid sick." Yet there is some evidence that the body, in its wisdom, has actually generated a hypothyroid state, in which pituitary sensitivity is down-regulated. TSH levels are usually normal but can be mildly elevated.[27] Indeed, in a recent prospective study of bone marrow transplant recipients, there was a reversible decline of TSH below normal levels with illness.[28] Correction of this functional hypothyroid state leads to increased protein catabolism[29] and seems to be unwarranted.[30]

Triiodothyronine levels fall quickly when peripheral conversion is blocked; the nadir occurs three to five days after an acute myocardial infarction, for instance. This low T_3 syndrome is distinct from primary hypothyroidism, in which T_3 levels are preserved at the expense of T_4 and TSH levels are considerably elevated by the time T_4 is overtly low (Figure 2). Severe illness can decrease elevated TSH levels in patients with underlying thyroid disease,[31] but only rarely, such as during dopamine infusion, is the TSH level lowered sufficiently to be falsely normal in a patient with primary thyroid failure.[32]

The low T_3 syndrome is easily distinguished from hypothyroidism, but with nonthyroidal illness, T_4 levels can also change. Total and even free T_4 concentrations are transiently increased to the hyperthyroid range in as many as 12% of acutely ill elderly patients.[33] Alterations in binding and decreased hormone metabolism may cause this state, called euthyroid hyperthyroxinemia.[34] Distinction from true thyrotoxicosis is best made retrospectively because the T_4 level returns to normal with recovery, usually after two to eight weeks. Thyrotropin-releasing hormone testing may prove discriminatory, but elderly men have a blunted TSH response. So only an absolutely flat TSH response will be diagnostic of hyperthyroidism.

When illness is more severe, however, a third syndrome of thyroid functional abnormality supervenes, the low T_4 syndrome (Figure 3). In these patients, usually under intensive care, the total T_4 level correlates to prognosis. A mortality rate of 84% was reported with T_4 levels below 3 μg per dl.[35] The free T_4 value, by dialysis, is often normal in such patients, but the total T_4 level is decreased by an acquired defect in binding to thyroxine-binding globulin. Apparently such severe illness nonspecifically activates membrane phospholipase A_2, producing arachidonic acid derivatives that interfere with T_4 binding.[36] Drugs, such as furosemide, also inhibit T_4 binding.[37] These patients do not have primary hypothyroidism, since TSH and free thyroxine levels are usually normal and the rT_3 value often high. In some cases, though, free T_4 is low, perhaps because of accelerated metabolic clearance.[38] Because such persons may actually have a functional central defect, distinguishing from pituitary or hypothalamic hypothyroidism is not always feasible. Reverse T_3 has been proposed as the best discriminatory test, but values overlap considerably between patients who are truly hypothyroid and those who are severely ill with nonthyroidal disease.[39]

Once the diagnosis of hypothyroidism is made, specific therapy is not necessarily urgent. Even in patients with myxedema coma, supportive therapy plays a larger role than does thyroid replacement. Older patients often have cardiac disease that can be worsened by overvigorous treatment. Combined with this, the metabolic clearance rate of thyroxine is about half what it is in younger persons, apparently related to lean body mass.[40] Thus, the replacement dose necessary to return the TSH to a normal level is considerably lower, as low

Low T_3 Syndrome	Hypothyroid
↓Conversion of T_4 to T_3	↑Conversion of T_4 to T_3
Normal TSH (rarely up to 15)	↑↑TSH
Low T_3, high or normal T_4	T_4 falls before T_3
↑rT_3	rT_3↓

Figure 2.—Triiodothyronine (T_3), thyroxine (T_4) and thyroid-stimulating hormone (TSH) responses in patients with the low T_3 syndrome and those with true hypothyroidism are compared. rT_3 = reverse T_3 (triiodothyronine)

Low T_4 Syndrome	Hypothyroid
↓Binding of T_4 to TBG	-------
↓T_4, ↓T_3	↓T_4, ↓T_3
Normal (usually) free T_4	↓Free T_4
Normal TSH	↑↑TSH
↑rT_3	↓rT_3

Figure 3.—Triiodothyronine (T_3), thyroxine (T_4) and thyroid-stimulating hormone (TSH) responses in patients with the low T_4 syndrome and those with true hypothyroidism are compared. rT_3 = reverse T_3 (triiodothyronine)

as 25 μg a day in some elderly patients.[41] The initial dose should be 25 to 50 μg, using the lower dose in a patient who has angina or congestive heart failure and increasing the dose 25 μg every four to six weeks. Certain patients, such as those in whom angina develops during replacement, fall into a metabolic trap. Compromise therapy is appropriate for them[42]; absolute normalization of the TSH is preferable but not essential.

Summary

What is the final diagnosis in the patient presented: hypothyroidism or nonthyroidal illness? The triiodothyronine level was low at a time when the T_4 was still within the normal range. Though the laboratory results do not absolutely discriminate, mild TSH elevation is the only point in favor of hypothyroidism. Free T_4 and rT_3 levels were not determined and might have been helpful, but the fact that the patient's condition improved before any expected benefit from thyroid replacement therapy strongly suggests that his illness was not due to primary hypothyroidism. Given the equivocal laboratory results, one appropriate course would have been to withhold hormone therapy and repeat testing after the patient's clinical state had become stable. Though occult disease may have been overlooked, the patient's response to hospital admission and to thyroid, folate and other nutritional replacement therapy was remarkable. Despite any missed diagnoses and untreated calcific aortic stenosis, this man is now doing very well.

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Chemotherapy for Herpes Simplex Virus Infections

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and formerly Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

LLOYD H. SMITH, JR, MD:* *The topic for this Medical Staff Conference is herpes simplex. Although the clinical presentation was first described nearly 2,000 years ago, it is only in recent years that effective antiviral therapy has become available. In this conference, Drs Kim Erlich and John Mills will review for us the clinical forms of herpes infection and the available approaches to treatment.*

History

KIM S. ERLICH, MD,† and JOHN MILLS, MD:‡ The name "herpes" is derived from the Greek word ερπειν *(herpein)*, which refers to the study of reptiles and in literal translation means "to creep." The term was used for centuries to describe a variety of cutaneous eruptions, many of which were probably not the result of a herpes simplex infection. Historical records indicate that true herpetic eruptions have probably been occurring in human populations since ancient times. The first actual description of classic herpes is credited to the Roman physician Heroditus who in 100 AD described "the herpetic eruptions which appeared about the mouth at the crisis of simple fevers." Genital herpes was probably first characterized by the French physician Astruc who in 1736 described the typical recurrent eruptions. The implication that genital herpes was a venereal disease seen in association with other venereal diseases was made in 1886 by Diday and Doyon.[1] It was not until 1921 that Lipschutz suggested that orolabial and genital herpes might be caused by "biologically related but etiologically different" agents. His hypothesis had been based on the observation that there was a difference in the severity of induced infections in animals using inoculum from either oral or genital lesions. Findings showing that orolabial and genital herpes were indeed caused by separate agents were published almost simultaneously in the early 1960s by Nahmias and Dowdle in the United States and Schneeweis in Germany[2] and have subsequently been confirmed by many other investigators. Since then, the wider use of improved diagnostic tests has documented the widespread prevalence of both herpes simplex viruses (HSV) type 1 and type 2 in the population, and we have come to realize the ability of both HSV-1 and HSV-2 to infect either the orolabial or genital areas.[3,4]

Although clinicians have for years attempted to treat HSV infections, our ability to offer objective benefit to an affected person is of relatively recent onset. Treatment of genital herpes was first discussed by Hutchinson who, in 1890, reported the "great benefit" seen in the management of the ailment by the long-term administration of a topical arsenic solution.[1] Since then numerous agents and treatment modalities have been reported, but until recently no true therapeutic benefit had been observed with any single regimen.

Herpes Simplex Virus

Both HSV-1 and HSV-2 are members of the Herpesviridae family. The other agents in this group that regularly cause human disease are cytomegalovirus, Epstein-Barr virus and varicella-zoster virus (Table 1). There are also numerous other members that cause disease in animals. Herpes viruses all have a similar structure, with a nucleoprotein core composed of double-stranded DNA, an icosahedral coat made up of 162 identical protein subunits and an outer membrane envelope composed of lipids and glycoproteins. HSV-1 and HSV-2 show about 50% homology in their DNA base sequences.

Both HSV-1 and HSV-2 replicate in a similar fashion. After attachment to the plasma membrane of the host cell, the virus loses its own envelope and enters the cytoplasm, releasing its nucleoprotein. The viral DNA enters the cell nucleus and directs the transcription of viral-specific messenger RNA, which in turn migrates to the cytoplasm where it specifies the synthesis of several classes of specific structural proteins and enzymes, including thymidine kinase and DNA polymerase. Virus assembly takes place in the cell nucleus, and the nonenveloped particles pass through the nuclear membrane where they obtain their envelope layer composed of

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membrane lipid and viral glycoprotein. The intact virus exits the cell by transportation to the cell surface in vacuoles, but, as the virus is cytocidal, the infection is usually fatal to the host cell.

Pathogenesis

Transmission of the HSV to a susceptible host usually occurs by direct contact with a person who is either excreting the virus from a clinically evident external lesion (primary or recurrent) or shedding the virus asymptomatically. Because the virus requires a moist environment for prolonged survival, transmission by fomites or inanimate objects occurs only rarely. Once transmitted to a new host, infection begins by inoculation of virus through susceptible mucosal surfaces or small breaks in the skin or mucosa. Current evidence suggests that the virus probably does not cause clinically apparent infection at the time of inoculation, but rather first multiplies and travels along distal sensory nerves to the peripheral nerve root ganglia.[5,6] After reaching the nerve root ganglia, a state of viral latency is established in which the viral genome can be detected in the host cell but virus replication and production of infectious viral particles do not occur. Only after latency is established can the virus then secondarily descend the peripheral nerves to cause infection in epidermal cells and result in clinically evident herpetic lesions.

The intermittent recurrences that are characteristic of HSV infection result from reactivation of latent virus in sensory ganglia. The mechanism for this phenomenon and the reasons for the wide variation in both the frequency and the severity of recurrent eruptions in otherwise normal hosts are being debated. One hypothesis is that the virus remains completely contained in its latent quiescent state until some external event such as stress, systemic illness or hormonal imbalance acts on the infected ganglion and stimulates reactivation. The viral genome changes from a latent state to a state of active replication, and the new virions travel down the peripheral nerve to infect the epithelial cells on the host surface, resulting in clinically apparent lesions.[4,5,7] An alternative hypothesis is that low-level reactivation is occurring continuously, but that under normal conditions a host's immune system successfully eradicates the small number of infectious viruses. Any of several temporary events at the site of infection could result in a local state of immunosuppression and allow for a recurrence of visible, symptomatic lesions or asymptomatic viral shedding.[8] Both theories are supported by various well-described characteristics of HSV infection, but neither has been proved conclusively.

TABLE 1.—*Common Clinical Illnesses Caused by Herpes Viruses*

Herpes Simplex Virus, Type 1
Gingivostomatitis
Pharyngitis
Recurrent orofacial eruptions ("fever blisters," "cold sores")
Keratoconjunctivitis
Encephalitis (adult)
Initial genital eruptions
Herpes Simplex Virus, Type 2
Initial and recurrent genital eruptions
Initial orolabial eruption
Disseminated neonatal infection
Encephalitis (neonate)
Aseptic meningitis (adult)
Varicella-Zoster Virus
Varicella (chickenpox)
Zoster ("shingles")
Encephalitis
Transverse myelitis
Pneumonia
Epstein-Barr Virus
Mononucleosis
Guillain-Barré syndrome
Cytomegalovirus
Mononucleosis
Congenital infection
Transfusion-related hepatitis
Guillain-Barré syndrome
Pneumonia, hepatitis, enteritis, retinitis (primarily in an immunocompromised host)

Clinical Characteristics

Both HSV-1 and HSV-2 are capable of causing infection at any mucocutaneous site, although HSV-1 is more commonly recovered from orolabial eruptions and HSV-2 is more commonly associated with genital lesions.[3,4,9] This pattern is particularly characteristic of persons with a long-standing history of recurrent disease. Many patients who have serologic evidence of a previous infection with HSV do not recall an illness consistent with either primary or recurrent illness[10]; reasons for this are poorly understood.

Orolabial Infection

Exposure to HSV-1 occurs frequently during childhood, and crowded living conditions are associated with higher rates of infection. The prevalence of antibody to HSV-1 in adults varies from 35% to 50% in higher socioeconomic groups to 80% or more in poorer, more densely populated communities.[9,11] Transmission occurs by inoculation of oral secretions onto the mucosal surface of a susceptible person, and disease begins after an incubation period of between 2 and 12 days.

The most common clinical manifestation of an initial primary orolabial infection in children is the development of gingivostomatitis. Symptoms can be so mild as to go unnoticed, but when present take the form of painful vesicular lesions occurring on the lips, tongue or buccal mucosa. There are often as many as 20 distinct vesicles that soon coalesce and rupture to form shallow ulcers covered with a whitish yellow necrotic material.[12] Fever and cervical lymphadenopathy are also frequently present. Excessive salivation and poor feeding are common findings in small children as the result of severe pain on swallowing. Involvement of the pharynx and tonsils also occurs, and sore throat may be the most prominent symptom of primary infection in adults.[13] The illness can be confused with streptococcal pharyngitis and may result in an inaccurate diagnosis and improper treatment. Visible lesions heal spontaneously over a seven- to ten-day period by reepithelialization with scarring. Viral latency in the trigeminal ganglia is established during this primary infection.

Subsequent recurrences of orolabial eruptions ("fever blisters") are spontaneous and associated with various other events, such as febrile illness, exposure to ultraviolet light or surgical manipulation of the trigeminal nerve and possibly stress or menstruation.[12] These systemic and local events act

as stimuli to trigger the virus to leave its latent state and cause clinical illness. Recurrent eruptions are usually preceded by a one- to two-day prodrome consisting of paresthesia and numbness at the area of impending eruption. Recurrences occur in the same general area as the initial primary lesions but are associated with less severe clinical symptoms and heal over a shorter period of time—usually between three and five days.

First Episode of a Genital Infection

Genital herpes is most commonly the result of infection with HSV-2, although as many as 15% of cases of initial genital infections are due to HSV-1. An initial genital infection due to HSV-2 in a person with serologic evidence of a previous HSV-1 infection is referred to as "nonprimary" infection and results in a milder clinical course with less severe symptoms than in those with no previous exposure to either HSV—that is, "primary" infection.[10]

HSV-2 is usually acquired as the result of genital contact with an infected person who most commonly is excreting the virus from active lesions that usually can be seen on careful physical examination. Transmission also occurs infrequently from asymptomatic virus shedding. The incubation period of genital infection is between 2 and 12 days—identical to that seen with HSV-1 orolabial infection. Local symptoms develop in virtually all patients with a first episode of genital infection, with more than 95% of men and 99% of women having painful vesical formation on the external genitalia.[13,14] Lesions begin as small papules that rapidly evolve to true vesicles filled with clear-white fluid. The vesicles have an erythematous base and are usually tender to palpation. During the initial outbreak, vesicles can appear as closely situated clusters or as widely spaced distinct lesions. The vesicles ulcerate rapidly, followed later by crusting and healing by reepithelialization. The time to complete healing of all lesions in cases of primary infection averages 16.5 days in men and 19.7 days in women, but occasionally patients may take four to six weeks to heal completely. Local itching, dysuria, urethral discharge and inguinal adenopathy are also commonly seen (Table 2). Dysuria is a more frequent complaint in women than in men and occurs even if the urethra is not involved by the infection. Local symptoms increase over the first week and gradually resolve over the second week of illness. Tender inguinal adenopathy develops late in the course of the illness and is usually the last symptom to resolve. Viral shedding can be readily shown during the first 10 to 12 days of clinical illness, but may persist for much longer. Viral shedding ceases as the lesions crust and begin to reepithelialize.[3,14]

In from 70% to 90% of women with an initial genital HSV infection, cervical inflammation develops and there is viral shedding from the cervical os. Patients may be asymptomatic or have purulent vaginal discharge. The cervix initially appears friable and erythematous and later may show shallow ulcerative lesions.

Systemic symptoms are seen in about a third of men and more than two thirds of women with a first episode of primary genital herpes. Frequent complaints include fever, headache, myalgias and general malaise. If present, constitutional symptoms appear within the first few days of the illness and are usually resolved by the end of the first week.

Complications of an Initial Genital Infection

Complications of HSV infection result from both local extension of infection and distant spread of virus to extragenital sites (Table 3). Aseptic meningitis is the most frequent complication, occurring in 36% of women and 11% of men with primary infection. Most patients with aseptic meningitis have headache, photophobia and stiff neck and have evidence of meningeal irritation on physical examination, but symptoms severe enough to require hospital admission are unusual. Lumbar puncture shows a slightly elevated opening pressure, a slightly elevated protein level and a normal or slightly low glucose level. A lymphocytic pleocytosis is commonly seen, with a total leukocyte count of between 5 and more than 1,000 cells per μl (mean, 550). Viral cultures of cerebrospinal fluid are usually negative, even when the specimen is obtained early in the illness.[15]

Autonomic nervous system dysfunction including neurogenic bladder, constipation, sacral anesthesia and impotence also occurs during a primary infection. Transverse myelitis has also been reported as a complication, but a permanent neurologic deficit is rare. Extragenital lesions are often found during the initial infection and may arise from neural spread (zosteriform herpes), blood-borne dissemination or by autoinoculation. Local extension that produces pelvic inflammatory disease also occurs.[14]

Recurrent Genital Infection

Recurrent genital eruptions result in a milder clinical course than that seen with the initial infection. About half of patients report prodromal symptoms beginning as long as 48 hours before the development of visible lesions. Paresthesias occur at the area of impending vesical formation or in a radicular pattern, although viral cultures are usually negative at this time. The prodrome is generally followed by the development of lesions at the site of the initial infection, although in some cases no eruption occurs—"false prodrome." The number of vesicles and the degree of discomfort are invariably less than that present during the initial outbreak. Dys-

TABLE 2.—*Physical Findings in Patients With Primary Genital Herpes Simplex Virus Infection**

Physical Findings	Frequency (%) Men	Women
Local pain	95	99
Tender inguinal adenopathy	80	81
Urethral or vaginal discharge	27	85
Dysuria	44	83
Constitutional symptoms—fever, headache, myalgias, malaise	39	68
Findings of meningitis	11	36

*From Nahmias and Roizman.[4]

TABLE 3.—*Complications of Primary Herpes Simplex Virus Genital Infection*

- Aseptic meningitis
- Autonomic nervous system dysfunction
- Transverse myelitis
- Disseminated spread to extragenital sites
- Pelvic inflammatory disease

uria, urethral discharge and vaginal discharge also occur much less frequently during recurrent episodes than during a primary infection. Vesicles begin healing rapidly and are completely encrusted by four to five days. Viral cultures of external lesions are usually negative at this time. Cervicitis occurs less frequently, with only 12% of women having positive cervical cultures. Systemic symptoms during recurrent genital eruptions occur very infrequently compared with the initial infection.[3,14]

Encephalitis

Encephalitis due to HSV occurs relatively infrequently, but this virus remains the most common agent responsible for nonepidemic cases of encephalitis. There appears to be no seasonal preference, and it affects all age groups in both men and women with equal frequency. Although some cases in adults appear to result as a complication of primary orolabial infection, most instances of HSV encephalitis occur spontaneously by reactivation of a previously latent type 1 disease. In contrast, HSV encephalitis in a neonate is usually the result of exposure to HSV-2 during passage through an infected birth canal and is often associated with disseminated infection.

The clinical presentation of HSV encephalitis is quite variable. The virus preferentially infects the orbitofrontal and temporal regions, possibly as the result of ascending spread along nerve fibers from the trigeminal ganglia to the anterior and middle fossae.[16] The most common clinical presentation is that of an acute encephalitis with early findings of fever, headache, nausea, mental state changes and signs of meningeal irritation. Temporal lobe findings, such as focal seizures, aphasia or olfactory hallucinations, are characteristic. The illness is usually rapidly progressive with confusion, disorientation, lethargy and focal or generalized seizures, followed quickly by coma. Localizing neurologic signs, such as transient hemiparesis and cranial nerve deficits, are also seen.[17] Examination of a cerebrospinal fluid specimen shows an increased intracranial pressure, elevated protein level and a lymphocytic pleocytosis. Erythrocytes are occasionally seen in the cerebrospinal fluid. Occasionally, however, patients have completely normal cerebrospinal fluid on examination. Viral cultures of a specimen of cerebrospinal fluid are positive in only a few percent of cases. An electroencephalogram or computed tomographic scan is abnormal in about 75% of cases and can be helpful in locating areas of involvement for diagnostic biopsy. Magnetic resonance imaging would be expected to be more sensitive, but clinical data are not available. Diagnosis can be made conclusively only by brain biopsy, the specimen typically showing hemorrhagic cortical necrosis with lymphocytic infiltration and the presence of characteristic intranuclear inclusion bodies. The virus is easily isolated from affected brain tissue and can also be identified by immunofluorescence and immunoperoxidase. Mortality in untreated patients is about 75%, with survivors often suffering from severe permanent neurologic deficits.[17-19]

Neonatal Infection

Infection in a neonate usually occurs as the result of delivery through an infected birth canal. Most, but not all, cases are caused by HSV-2. The overall incidence of neonatal infection is estimated at between 1 in 3,000 and 1 in every 30,000 live births. Clinical manifestations of neonatal infection range from local lesions of the skin, eye, mouth or central nervous system to severe, widespread dissemination involving visceral organs. Encephalitis can occur as an isolated finding or as a manifestation of disseminated disease. Meningoencephalitis occurs in 50% or more of infants with neonatal infection and may be the result of viremic spread.[9,18]

Clinical findings usually appear during the first week of life but may not be present until as late as 3 weeks of age. Lethargy, poor feeding, abnormal temperature regulation, hepatomegaly and respiratory distress are early findings. As the illness progresses, signs of increased intracranial pressure with bulging fontanelles, generalized or focal seizures refractory to medication, cranial nerve palsies and flaccid or spastic paralysis are seen. Examination of the cerebrospinal fluid in infants with meningoencephalitis usually shows abnormalities, but it may not be abnormal immediately after birth. Lymphocytic pleocytosis, elevated protein and normal or slightly depressed glucose levels are common findings. Unlike an adult patient with encephalitis, infants with HSV infection usually have virus isolated from their cerebrospinal fluid.

Prevention of neonatal HSV infection can be achieved by avoiding birth through an infected canal. An infant at term whose mother has active genital lesions should be delivered by cesarean section if the membranes have not been ruptured for an extended period of time, in which case ascending infection may have already occurred.[20] A small number of pregnant women may shed the virus from their cervix asymptomatically and therefore may not present with visible, external herpetic lesions. Women with a history of initial or recurrent genital herpes should obtain weekly cervical viral cultures during their final month of pregnancy and undergo delivery by cesarean section if the most recent cultures are positive for HSV or if external or internal lesions consistent with HSV infection are present at the time of delivery.

Diagnosis

Patients with suspected primary or recurrent HSV infection should have the diagnosis confirmed virologically. Intact vesicles can be mechanically ruptured and the fluid cultured for virus. The erythematous base of a suspicious broken vesicle can be scraped gently and will frequently yield virus on culture. Giemsa or Wright's stain of the scraping will show multinucleated giant cells and Cowdry type A intranuclear inclusion bodies (Tzanck's test). Fluorescein-labeled antibodies are also available to detect viral antigens on the surface of infected cells; these staining techniques are more sensitive and specific than the Tzanck's smear.

Viral culture is done by inoculating a fluid or tissue specimen into one of several available tissue culture cell lines. Typical cytopathic effects are usually observed within one to two days and progress rapidly due to the release of virus into the media from infected and lysed cells. Both HSV-1 and HSV-2 may show similar cytopathic effects in infected cell lines and cannot be reliably differentiated by culture alone. Differentiating between HSV-1 and HSV-2 is usually done using commercially available fluorescein-labeled monoclonal antibodies, although other procedures such as polyacrylamide gel fingerprinting of restriction endonuclease digests of DNA can also be used.

Serum antibodies to HSV can be detected by numerous techniques including complement fixation, neutralization and enzyme-linked immunoassay. As there is a high degree of antigenic relatedness between HSV-1 and HSV-2, infection with one type usually induces antibody that is reactive against both. Newer investigational serologic tests can define the type of infecting virus in 50% to 75% of cases, but in the remaining patients the virus type cannot be determined. The most appropriate use of serologic testing is to differentiate primary from recurrent infection by comparing acute and convalescent antibody titers. In the acute stage of primary infection, the patient lacks antibody in the specimen but a significant (fourfold or greater) rise occurs in a specimen taken during convalescence. In a nonprimary initial infection, antibody is present in the initial specimen, but a significant rise is seen during convalescence. Recurrent HSV infections are associated with a stable antibody titer in more than 95% of cases.[21]

Treatment

A variety of therapeutic modalities have been advocated over the years for cases of HSV infection, but most regimens have been shown to be ineffective or deleterious when subjected to careful clinical study. In the past few years a few agents have proved to be both safe and effective in the treatment of specific acute HSV infections, and have enabled clinicians to have a significant impact on acutely ill patients. Unfortunately, the regimens so far examined do not have any effect on viral latency, and thus have no effect on the future pattern of recurrences.

Acyclovir

The most recently available antiherpetic agent, acyclovir (9-[(2-hydroxyethoxy)methyl]guanine), is an acyclic nucleoside analogue of guanosine. Its activity against HSV-infected cells is due to its selective phosphorylation by the viral thymidine kinase to acyclovir monophosphate. This monophosphate intermediate is subsequently phosphorylated by cellular kinases to the triphosphate, which is the active antiviral agent. Acyclovir triphosphate acts as a selective inhibitor of viral DNA polymerase and is slightly more active against HSV-1 than HSV-2. Both HSV types are about ten times more susceptible than varicella-zoster virus.

Acyclovir is minimally protein bound and distributes into all tissues, including cerebrospinal fluid. The major route of elimination is by the kidney, and the serum half-life in patients with normal renal function is about two to three hours. After an intravenous infusion, most of the drug can be recovered unchanged in the urine, with a small amount metabolized to an oxidized form. Acyclovir accumulates in patients with impaired renal function unless the dosage is modified. The serum half-life in an anephric patient is about 20 hours, and the drug is effectively removed by hemodialysis.[22]

Intravenous, oral and topical preparations of acyclovir are available and have undergone extensive clinical evaluations in both immunocompetent and immunocompromised persons with HSV infections. Effectiveness depends on the route of administration, dosage used, duration of treatment, immune state of the host and whether the infection is a first episode or a clinical recurrence.

Intravenous Acyclovir

Intravenous administration of acyclovir to immunocompetent or immunosuppressed persons with primary infection dramatically shortens the course of the illness. Corey and colleagues compared a regimen of acyclovir given intravenously at 15 mg per kg a day for five days with administration of a placebo in 31 normal persons with a severe first episode of genital herpes.[23] Acyclovir-treated patients were shown to have a greatly decreased duration of viral shedding from external lesions (2 versus 13 days) and almost immediate sterilization of pharyngeal, cervical, urethral or urine cultures. External lesions healed faster in the acyclovir-treated group (lesions crusted in 6 versus 13 days), and the duration of both local and systemic symptoms was decreased. Acyclovir therapy also caused a sharp decrease in the number of new lesions forming after therapy was begun. Unfortunately, no differences in frequency or severity of subsequent recurrences were noted. Comparable results were observed by Mindel and Adler.[24]

Recurrent, chronic, ulcerative, mucocutaneous HSV infections in patients with defective cellular immunity also respond well to intravenous administration of acyclovir. Preliminary uncontrolled trials had suggested the efficacy of giving acyclovir intravenously to bone marrow transplant patients with herpetic eruptions,[25] and subsequent double-blinded, placebo-controlled trials verified this observation.[26,27] Wade and associates randomly allocated 34 bone marrow transplant patients with mucocutaneous HSV infections that developed while they were receiving immunosuppressive therapy to receive either acyclovir, 750 mg per m^2 body surface area, or placebo for seven days. Acyclovir therapy produced a substantial reduction in the duration of viral shedding (3 versus 17 days), duration of clinical symptoms (10 versus 16 days) and time for healing of lesions (14 versus 28 days). One unexpected finding in this population was that, compared with the placebo group, the patients treated intravenously with acyclovir had a shorter interval of time until their next clinical outbreak, and this outbreak was more severe.[26]

Prophylactic intravenous administration of acyclovir to patients with serologic evidence of a previous HSV infection has been shown to prevent active recurrences during immunosuppressive therapy. Saral and co-workers reported the results of a prospective, randomized, placebo-controlled trial of intravenously given acyclovir, 750 mg per m^2 per day, as prophylaxis in bone marrow transplant recipients with serologic evidence of a previous HSV infection.[28] The regimen of acyclovir or placebo was begun three days before marrow transplantation and continued for a total of 18 days. Herpes did not develop in any of the acyclovir-treated patients, whereas seven of ten patients receiving placebo had clinical and culture-confirmed herpetic eruptions at an average of 11 days after entry into the study (range, 7 to 17 days). An additional patient showed asymptomatic viral shedding. After discontinuing therapy, five of the ten acyclovir-treated patients had clinical recurrences, and two additional patients shed the virus asymptomatically. Other studies have confirmed that first recurrences following acyclovir prophylaxis in immunosuppressed patients occur earlier and are more severe than in placebo-treated patients.

Intravenous acyclovir has been reported to be effective in

treating patients with encephalitis and was unequivocally superior to the standard regimen of vidarabine in a comparative trial conducted in Sweden.[29] A similar trial was recently completed in the United States, and preliminary analysis has suggested the superiority of acyclovir over vidarabine.[30] Data from a prospective trial comparing vidarabine with acyclovir for treatment of disseminated HSV infection in neonates are not yet available.

Oral Acyclovir

Acyclovir for administration by mouth is available in 200-mg capsules, and about 20% of the ingested dose is bioavailable. A placebo-controlled study showed that immunocompetent patients with a first episode of genital HSV infections had a pronounced beneficial effect when treated with oral acyclovir, 200 mg five times a day for a ten-day period.[31] The duration of viral shedding, new lesion formation and duration of genital lesions were significantly reduced in both male and female treated patients. Also noted was a significant reduction of subjective clinical symptoms in patients who received acyclovir, but no differences in frequency or severity of subsequent recurrences have been observed. The drug also has a beneficial therapeutic effect, albeit less dramatic, in patients with recurrent genital HSV infection. Formal trials in patients with primary or recurrent orofacial HSV infection have not yet been reported; presumably the results will be comparable to those seen with genital infection.

Prophylactically administering acyclovir three times a day by mouth dramatically reduces the frequency of recurrent genital HSV infection.[32,33] Although continuous oral administration does not eliminate recurrences completely, those that do occur are somewhat shorter in duration and are associated with a shorter period of viral shedding. Some viral isolates from specimens obtained while a patient was receiving acyclovir therapy have developed relative acyclovir resistance induced by the loss of thymidine kinase (thymidine kinase-deficient mutants).[34] Once oral acyclovir therapy is discontinued, however, the viral isolates obtained from recurrent lesions in these patients regain thymidine kinase and become fully susceptible to acyclovir. Whether this represents mutation of the virus back to a sensitive variant or whether the more resistant strain remains present in a latent form is unknown. In HSV-infected mice maintained long term on subtherapeutic doses of acyclovir, acyclovir-resistant, thymidine kinase-negative mutants develop.[35] These resistant strains appear to be somewhat less pathogenic for animals and are less likely to establish neural latency.[35,36] These observations suggest that although acyclovir-resistant strains may be recovered from clinical lesions while a patient is receiving therapy, these resistant variants may be relatively avirulent, and the latent virus may remain fully susceptible.

Oral acyclovir chemoprophylaxis also protects immunocompromised patients from recurrences of HSV infection, but the drug does not appear to be as protective when given orally as when given intravenously, although formal comparative trials have not been done.[37,38] Therapy has been continued for as long as six months in this group of patients, with continued suppression of clinical recurrences.

Topical Acyclovir

Double-blinded, placebo-controlled trials comparing topical application of 5% acyclovir ointment in polyethylene glycol to applying the polyethylene base alone have shown a therapeutic response that differs depending on whether the outbreak is primary or recurrent and on whether the patient is male or female. Applying topical acyclovir to first-episode, primary genital eruptions has been shown to result in a modest decrease in the duration of viral shedding in both men and women. The mean duration of local symptoms (pain, itching, dysuria) is slightly shortened by acyclovir application, as is the time until healing of lesions present at the onset of therapy. The time until complete healing of all lesions, however, including those new lesions that develop while therapy is ongoing, is not affected by topical acyclovir.[39] There also appears to be no effect on the development of viral latency and no reduction in the frequency of subsequent recurrent genital eruptions.

Applying acyclovir topically has virtually no apparent therapeutic benefit in patients with recurrent genital herpes. Results from several studies have shown no consistent benefit other than a slightly shortened duration of viral shedding.[39,40] Because these trials had been designed for treatment to be instituted after clinical lesions had already developed, it was suggested that an earlier onset of therapy (during the prodrome period) might result in a demonstrable beneficial effect. A double-blinded, placebo-controlled study was subsequently done that allowed for "patient-initiated" application of acyclovir to the site of expected recurrent lesions during the prodrome period. The results indicated only a slight decrease in the duration of viral shedding in female patients (1.1 versus 2.0 days) and no effect on the overall clinical course.[41]

Other Antiviral Agents

Adenine arabinoside (vidarabine, ara-A) is an analogue of the nucleoside adenine deoxyriboside and is active in vitro against many viruses, including HSV. Its mechanism of action is incompletely understood, but the compound undergoes phosphorylation to a triphosphate form, which is a potent inhibitor of viral DNA polymerase. The drug is eliminated by the kidney and has a serum half-life of about 3.5 hours. Vidarabine is poorly tolerated, and gastrointestinal, neurologic and hematologic toxicity occurs commonly. The drug is poorly soluble and requires a large amount of fluid for administration; thus, hyponatremia is also common.

Vidarabine has good in vitro activity against HSV, and at a dose of 15 mg per kg per day was the first agent shown to reduce the mortality of patients with HSV encephalitis from 70% to 30% in a randomized, placebo-controlled trial.[17] Further evaluation has also shown its effectiveness in the treatment of neonates with disseminated disease,[18] and a topical formulation is useful in the management of cases of HSV keratoconjunctivitis. This drug has largely been replaced by acyclovir, which is more effective, easier to administer and less toxic.

Iododeoxyuridine (5-iodo-2′-deoxyuridine, IUDR) is a nucleoside analogue of thymidine that has been effective in managing HSV keratoconjunctivitis when applied topically. The drug undergoes phosphorylation in the viral-infected cell and is incorporated into viral DNA in the place of thymidine. Topical application is effective only for localized eye infection, and it has not been shown to be effective in the treatment of orolabial or genital lesions. Systemic therapy with idoxuridine for HSV encephalitis has been ineffective and toxic.

TABLE 4.—*Treatment Regimens for Herpes Simplex Virus Infection by Location*

Clinical Presentation	*Antiviral*	*Duration*	*Relative Efficacy*
Genital—first episode (outpatient)	Acyclovir 200 mg PO 5 × d	Until lesions are crusted	Very good
Genital—first episode (admitted to hospital)	Acyclovir 5 mg/kg IV q 8 hr	Until lesions are crusted	Very good
Genital—recurrent	Acyclovir 200 mg PO 5 × d	Until lesions are crusted	Fair
Genital—frequent recurrences	Acyclovir 200 mg PO 3 × d	Daily for up to 6 mo	Excellent
Encephalitis	Acyclovir 10 mg/kg q 8 hr IV	10 d	Excellent
	Vidarabine 15 mg/kg/d IV	10 d	Good
Neonatal infection	Acyclovir 10 mg/kg q 8 hr IV	10-14 d	Fair
	Vidarabine 15 mg/kg/d IV	10-14 d	Fair

IV = intravenously, PO = by mouth

Clinical Management of Herpes Simplex Disease

Initial Genital Infection

Most patients presenting with a possible first episode of genital eruptions (either primary or nonprimary) will appear ill and uncomfortable but will not be sick enough to require hospital admission. These patients should receive counseling and education on the nature and latency of their infection and be given a course of oral acyclovir, 200 mg every four hours while awake (five times a day), until the lesions have crusted. Acyclovir therapy should not be continued indefinitely at this time as most patients will not have frequent or severe recurrences after their initial episode (Table 4).

Patients with an initial genital infection who have severe local or systemic symptoms, who require parenteral analgesics or in whom incapacitating neurologic complications such as urinary retention develop should be admitted to hospital. These patients should receive acyclovir intravenously, 5 mg per kg every eight hours while in hospital; when the patient is ready for discharge, administration of acyclovir should be continued by mouth until all visible lesions have crusted.

Recurrent Genital Infection

Not all patients with recurrent genital eruptions require treatment. Many infected persons have clinical recurrences only infrequently, and the illness may be so mild as to go virtually unnoticed. Acyclovir therapy for each recurrence would appear to offer little benefit in this situation, and prophylaxis (requiring continuous, three-times-a-day administration of acyclovir) would seem to be unnecessary. Patients with frequent or severe recurrences, however, will probably wish to treat each recurrence with a regimen of acyclovir, 200 mg by mouth five times a day, until lesions have crusted. The drug therapy should be begun as early as possible (preferably at the time of the prodrome) for maximum benefit. Once the diagnosis of recurrent herpes has been established, these patients can treat most recurrences themselves, with physician visits every 6 to 12 months to monitor toxicity and the course of the disease.

Acyclovir chemosuppression should be reserved for those patients with severe or frequent recurrences who suffer a significant amount of morbidity (physical or psychological) from their recurrent eruptions. The decision to place a patient on an ongoing suppressive regimen must be made on an individual basis, with the patient well aware of the risks and limitations of chemosuppression, as well as its cost (about $1.50 a day). The effects of long-term acyclovir administration in humans are not yet known, and chemosuppression is not recommended for longer than six months at this time. The patient must be made aware that the first recurrence after a period of chemosuppression may occur earlier and may be more severe than those experienced previously. The recommended dose is 200 mg three times a day.

Encephalitis

Until recently vidarabine (15 mg per kg per day for ten days) was the treatment of choice for patients with HSV encephalitis.[17] A recent comparative trial, however, showed that acyclovir therapy (10 mg per kg every eight hours for ten days) was more effective and less toxic than vidarabine.[29] Acyclovir requires less fluid for administering than does vidarabine, an additional advantage in a patient with cerebral edema due to encephalitis. Clinicians should consider the possibility of HSV infection in any patient with meningoencephalitis and should begin acyclovir therapy immediately if there is any possibility of herpes being present. Brain biopsy can be done successfully for diagnosis as long as 48 to 72 hours after therapy has been started. Early therapy improves the long-term outcome, which is directly correlated with the patient's mental state at the time treatment is begun.

Neonatal Infection

Infants born by vaginal delivery to infected mothers with either clinically apparent lesions or asymptomatic viral shedding should have cultures of specimens of cerebrospinal fluid, urine, conjunctivae, oropharynx and skin for HSV. Treatment should be instituted immediately and continued if cultures are positive or if signs of active disease develop. Some authorities recommend starting therapy immediately in every infant suspected of being infected and discontinuing it only if cultures are negative. The justification for this course of action is that early therapy (before neurologic deterioration has occurred) probably favorably influences outcome. We prefer therapy with acyclovir, 10 mg per kg given intravenously every eight hours for 10 to 14 days, although vidarabine therapy is also effective.

Immunocompromised Host

A patient with an altered immune system and either primary or recurrent HSV infection presents a special management problem. Herpetic eruptions can be quite extensive, with severe localized symptoms and widespread dissemination. Spontaneous healing of localized outbreaks occurs much more slowly than in immunocompetent persons or does not occur at all. Most patients will respond to treatment with oral (200 mg five times a day) or topical acyclovir (applied five times a day). Admission to hospital for intravenous administration of acyclovir (5 mg per kg every eight hours) is war-

ranted only for severe eruptions in patients who cannot take drug by mouth, or who fail to respond to orally given therapy. As this latter occurrence is rare, the presence of acyclovir-resistant HSV (which may occur with greater frequency in immunocompromised patients than in normal patients) should be considered. Patients with frequent or severe recurrences will probably benefit from long-term suppressive therapy with acyclovir, 200 mg by mouth three times a day. Higher doses (400 to 600 mg three times a day) should be used if breakthrough recurrences occur at the lower dose.

Summary

Infections due to herpes simplex virus type 1 and type 2 result in a wide spectrum of clinical illness ranging from a state of asymptomatic viral shedding to widespread dissemination or encephalitis. The propensity of the virus to achieve a latent state in nerve root ganglia permits spontaneous recurrences of clinically symptomatic lesions. Herpes simplex infection is usually suspected in a patient with typical external lesions and should be confirmed by identifying the virus in culture, by immunofluorescence or identifying by other sensitive and specific methods. Diagnosis of encephalitis due to herpes simplex virus still requires confirmatory brain biopsy for histopathology, detection of viral antigens and viral culture. Therapy with acyclovir has been shown to be beneficial in patients with both localized HSV eruptions and disseminated illness. Persons with a first episode of genital herpes have a dramatic reduction in local symptomatology, viral shedding and systemic symptoms when treated with either oral or intravenous administration of acyclovir; topical application of acyclovir results in a more modest local response. Recurrent genital herpetic eruptions can be treated effectively with acyclovir given orally or intravenously in both immunocompetent and immunosuppressed patients. No beneficial effect with the use of topical acyclovir in these patients has been shown. Acyclovir is superior to vidarabine in the treatment of HSV encephalitis and also may be the agent of choice in the therapy for disseminated neonatal disease.

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Epitomes

Important Advances in Clinical Medicine

Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in preventive medicine and public health that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Preventing Influenza in the Elderly

STUDIES HAVE consistently shown that the elderly and those with certain medical conditions are at the highest risk for morbidity and mortality due to influenza virus infections. Influenza and pneumonia remain the fourth leading cause of death in the elderly. The US Public Health Service's Advisory Committee on Immunization Practices recommends that the elderly and other high-risk groups be vaccinated annually against influenza infection. However, the recommendation has been based primarily on extrapolated efficacy data from younger populations, rather than on data directly documenting vaccine efficacy in elderly populations. Also, the recommendation is generally not followed. In national surveys, only about 20% of high-risk patients are vaccinated annually.

Vaccination of nursing home elderly patients may be particularly important. Epidemics of influenza in nursing homes are associated with high morbidity and mortality, and more data have accumulated regarding vaccine efficacy in this setting. In a recent study of the influenza A epidemic in Michigan between December 1982 and March 1983, vaccinated nursing home residents were less likely to become ill, have development of pneumonia, be admitted to hospital or die. Although the reported vaccine efficacy of 28% to 37% inferred from attack rates was considerably lower than usual estimates of efficacy, these results suggest that, at least in nursing home patients, influenza vaccination may attenuate infection even if it does not prevent it. These data also show significant noncompliance. Even though physicians routinely ordered flu shots for the Michigan nursing home patients, 46% of patients were not vaccinated because they refused or because relatives did not give consent.

In a recent longitudinal, prospective study of attitudinal risk factors for noncompliance, patients' attitudes about influenza vaccine effectiveness, vaccine side effects and their physicians' opinion of influenza vaccination strongly predicted compliance with flu shots in two consecutive flu seasons. Overall, patients' behavior regarding flu vaccination was consistent during the two flu seasons. Compliance changed in 10% to 15% of patients, primarily associated with changes in attitudes about side effects of influenza vaccine. A combination of physician counseling and efforts to identify and contact high-risk patients may improve compliance. Annually mailing letter reminders combined with physician counseling have gradually increased a clinic's vaccination rates to more than 70%.

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Clinical Basis for Treating Presumptive Chlamydial Infection

Chlamydia trachomatis is our most common sexually transmitted pathogen and is responsible for an estimated 3 million cases of infection annually in the United States. The most common presentation is nongonococcal urethritis in men, but the most important consequences of chlamydial infection—acute salpingitis, tubal factor infertility and probably ectopic pregnancy—occur in women. *C trachomatis* also causes inclusion conjunctivitis and pneumonia in young infants.

The accurate diagnosis of chlamydial infection, not available in most clinical settings, depends on expensive tissue culture isolation procedures. Because chlamydial infections

occur at high rates in certain clinical conditions, the Centers for Disease Control recommend antichlamydial therapy—500 mg of tetracycline four times a day for seven days—for persons with those findings and for their sex partners.

Heterosexual patients with gonorrhea and their partners should be treated for chlamydial infection because about 20% of men and 40% of women with gonococcal infections also have chlamydial infection.

Other conditions that call for presumptive therapy in men are nongonococcal urethritis and epididymo-orchitis; treatment should be given for at least ten days. For women, mucopurulent endocervicitis or acute salpingitis call for antichlamydial therapy, salpingitis requiring multiple drug therapy to cover all pathogens. Again, therapy should be given for at least ten days.

Infants with inclusion conjunctivitis or *Chlamydia* pneumonia and their parents should also be treated. Erythromycin is the drug of choice for treating infants and pregnant women.

Chlamydial cultures should be used preferentially for testing persons who would not be treated on a presumptive basis. Groups benefiting from screening include young, particularly adolescent, sexually active women and pregnant women in socioeconomic circumstances that suggest a high risk for sexually transmitted disease.

Recently introduced nonculture methods may make chlamydial diagnosis more widely available and less expensive. More experience is needed, however, to assess the performance profiles of these tests to best determine how they can be used. Because all nonculture methods have some false-positive results, they should not be used for screening in low prevalence settings.

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Polysaccharide Vaccine for Preventing *Hemophilus influenzae* Type b Disease

A POLYSACCHARIDE VACCINE for preventing invasive diseases caused by *Hemophilus influenzae* type b (Hib) was recently licensed by the US Food and Drug Administration (Hemophilus b polysaccharide vaccine; b-Capsa I, Mead Johnson).* *H influenzae* type b is the leading cause of bacterial meningitis in the United States and an important cause of other systemic illness. An estimated 20,000 cases of *H influenzae* type b occur annually; 1 out of 200 children will have an episode of invasive *H influenzae* type b before reaching their fifth birthday. In spite of antibiotic therapy, 5% to 10% of patients die and 25% of the patients with meningitis who survive will have neurologic sequelae. The incidence of this disease is highest in young children and declines rapidly with increasing age. In two recent studies, there was a significantly increased risk of primary *H influenzae* type b in children attending day care. Children with asplenia, sickle cell disease, Hodgkin's disease and antibody-deficiency syndromes are also at increased risk of this disease.

The recently licensed Hib vaccine consists of the purified polysaccharide capsule of the organism. Like other capsular polysaccharide vaccines (meningococcal and pneumococcal vaccine), the vaccine produces minimal adverse reactions, but it is poorly immunogenic in young children. The vaccine elicits an antibody response likely to be protective in children 18 to 20 months old; geometric mean antibody titers rise with age. A prelicensure clinical trial in Finland showed 90% efficacy in children 18 to 71 months of age, but no efficacy in children younger than 18 months. There were insufficient numbers in each age category in this study to assess efficacy in children 18 to 23 months of age, although no cases occurred in the four-year follow-up of 4,000 children in this age group who received the vaccine. An efficacy trial is currently under way on a new Hib vaccine consisting of a covalently linked polysaccharide protein conjugate that may be efficacious in young children; if effective, this vaccine could be available as early as 1988. In the interim, the 25% to 35% of cases of invasive *H influenzae* type b in older children is potentially preventable by using the polysaccharide vaccine. The US Public Health Service Advisory Committee on Immunization Practices therefore recommends the universal use of the vaccine at 24 months of age; vaccination at 18 months is suggested for children at high risk of disease, including those in day care. Additional information regarding the duration of antibody response is needed to define the possible need for and timing of a second dose of vaccine in children vaccinated at 18 to 23 months. The vaccine is not recommended for children younger than 18 months. Immunizing children older than 24 months who have not yet received the type b vaccine should be based on their risk of disease. The vaccine is not recommended for preventing otitis media or upper respiratory tract disease, since these are due predominantly to unencapsulated *H influenzae*.

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*Use of the trade name does not constitute endorsement by the US Public Health Service.

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Preventing Low Birth Weight

INFANTS WEIGHING 2,501 grams or less at birth are 40 times more likely to die during the first four weeks of life than are infants with a normal birth weight, and they have increased risks for major and minor handicapping conditions, as well. Unfortunately, the decline between 1965 and 1980 in the infant mortality rate in the United States (from 24.7 to 13.1 per 1,000 live births) was not accompanied by a parallel decline in the rate of low-birth-weight infants. Lower infant

mortality is due primarily to improved survival of low-birth-weight infants, involving high-cost neonatal intensive care and carrying uncertain prospects for childhood development.

According to a new report from the Institute of Medicine, sustaining the decline in infant mortality will require major actions to prevent low birth weights, emphasizing better maternal health, good nutrition for pregnant women and systematic and early prenatal care. During the early 1980s, federal support for such low-cost, high-yield programs has been limited. An analysis using census tract income data and birth tapes from the state of Washington has shown that the proportion of births receiving no or late prenatal care, the proportion of low-birth-weight infants and the prevalence of maternal anemia all increased in the low-income populations. Such findings have given renewed impetus to state-level initiatives to provide Medicaid eligibility, to enhance primary care and case management and to assure nutritional supplementation for poor pregnant women.

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Preventing Osteoporosis

Loss of bone mass is a universal phenomenon of aging. Clinically significant osteoporosis—that associated with fracture in the absence of major trauma—is primarily a disease of postmenopausal white women. Men and black women are at much lower risk. In the United States, one in four white women will have an osteoporotic spinal fracture by the age of 60 and by the age of 90, one in five will have an osteoporotic hip fracture. One third of patients die within a year of an osteoporotic hip fracture and another third suffer chronic disability.

In addition to age, gender and race, other probable risk factors for osteoporosis include height, leanness, cigarette smoking, lack of weight-bearing exercise and low calcium intake. General recommendations to prevent or delay osteoporosis for both men and women of all races include not smoking, moderate exercise (extreme exercise such as marathon running may cause osteoporosis in some young women) and increased calcium and vitamin D intake.

For postmenopausal women, the currently recommended daily calcium intake to retard osteoporosis is 1.5 grams a day. This dose can be accomplished by drinking five 8-oz glasses of milk (preferably low fat or skim) or by the use of calcium supplements (preferably calcium carbonate). Milk has the advantage of being an excellent source of vitamin D. Bone meal products should be avoided because they may contain contaminants such as lead. Adequate calcium intake should begin early in life because it may lead to a greater bone mass, thus delaying the development of clinically significant osteoporosis in later years. Calcium supplements have been shown to improve calcium balance and retard bone loss when begun as late as eight years after menopause, however.

For postmenopausal women the single most effective preventive measure is estrogen-replacement therapy. Numerous clinical trials, primarily in women who have had oophorectomies, have shown that bone loss can be prevented with supplemental estrogen. The minimum effective dose of conjugated equine estrogen, the most commonly prescribed noncontraceptive estrogen in the United States, is 0.625 mg per day. Optimal results are achieved when estrogen is begun within a year of menopause, but cessation of bone loss and some increase in bone density may be achieved when estrogen therapy is begun six or more years after menopause. Bone loss resumes at its previous rate when estrogen is discontinued, so long-term use is necessary. The osteotrophic effects of estrogen are not impaired when a progestin is added, a practice frequently followed to reduce the risk of estrogen-associated endometrial cancer. Less is known about the long-term risks of progestin than estrogen alone, however.

There is mounting evidence that estrogen used alone may reduce ischemic heart disease mortality, possibly mediated by estrogen-induced increases in high-density-lipoprotein cholesterol. This effect is lost or modified by adding a progestin. There are no long-term studies that compare the effects of estrogen-progestin on death or cardiovascular disease risk in treated and untreated postmenopausal women. If the use of only estrogen reduces ischemic heart disease risk, this health benefit would be much greater than the risk of endometrial cancer, which is far less common and less lethal than heart disease. In that case, the use of estrogen only would be preferable to the estrogen-progestin combination.

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Toxic Materials and Practicing Physicians

Physicians are increasingly more likely to encounter patients who are ill from exposure to a known toxic material, ill from suspected exposure to a toxic material (either the toxicity, the exposure or both may be unknown) or not ill but concerned about an exposure. These situations can be trying for both patient and physician for many reasons. First, the scope of the toxic materials issue is wide and getting wider all the time ("doesn't everything cause cancer, Doctor?"). Second, current theory suggests that carcinogens do not have thresholds below which the probability of disease is zero, though it may be miniscule. Third, our hindsight concerning exposure conditions once thought to be trivial has made us very cautious about giving reassurance in the face of great uncertainty (such as with the swine flu vaccine).

The scope of the issue ranges all the way from occupational exposure to cyanide (high dose, known great toxicity) or asbestos (high dose, known carcinogen), to consuming wild ducks shot near Kesterson National Wildlife Refuge (central California) that may have elevated residues of selenium (low-to-zero dose, uncertain toxicity), to simply residing in a neighborhood within a couple of miles of a hazardous waste site (unknown dose, unknown agents, unknown

toxicity). With this wide a range of known and unknown possibilities and unknowables, patients want help dealing with their perceptions of health with respect to toxic substances. In addition, medical professionals have specific occupational exposures of concern to them (nurses and pharmacists making up and administering cancer chemotherapeutic agents, x-ray personnel, operating room staff exposed to ethylene oxide sterilizing gas and anesthetics and so forth).

The history of modern medical science teaches epidemiologists that the first clue to previously unknown agent-host-environment relationships often comes from an alert and curious clinician who sees a case in a novel light and shares these thoughts with others who can help find additional examples and pursue the matter further. This process can be facilitated when those of us responsible for studying these problems in the public health community make ourselves available to share what information we have and help clinicians provide responses to patients who are anxious, ill or both. A call to a county health department is always in order. At the state level, such assistance is usually available from the departments of health (drinking water, hazardous waste, food and drug contaminants, pesticides, synthetic chemicals, carcinogens and teratogens, general environmental and occupational exposures, indoor air contaminants, metals and the like); agriculture (agricultural chemicals, toxic plants); industrial relations (occupational exposures and conditions); the air quality office (constituents of air pollution in various locations); the water quality office (constituents of ground and surface water pollution in various locations), and elsewhere. In California, the first call might best be directed to the new Tox-Info Center, a joint effort of the California Department of Health Services and the University of California at San Francisco (hotline 800-233-3360 is toll-free in California).

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Cancer In Situ of the Uterus and Cigarette Smoking

RECOMMENDATIONS FOR THE frequency of Papanicolaou tests have been based on the assumption that cancer of the uterine cervix is a venereally transmitted disease. Young women who are sexually active are advised to have a smear taken regularly. Over the past eight years several studies have raised the possibility that cigarette smoking is an independent risk factor for cervical cancer and is associated with a substantially higher risk than seen in women with multiple sexual partners.

In 1977 Winkelstein and co-workers pointed out the association seen between cigarette smoking and cancer of the uterine cervix in the data collected by the National Cancer Institute between 1969 and 1971. They suggested further research. Since that time, four carefully designed case-control studies testing this hypothesis have been completed. All have found that cigarette smoking is a risk factor for cancer of the uterine cervix independent of sexual activity. The risk was estimated at between 8 and 17 times greater, and has been found for dysplasias of the cervix as well as in situ carcinoma. Winkelstein and associates reviewed the evidence again in 1984 and concluded that there likely was a causal connection between smoking and cervical neoplasia.

In 1985 Sasson and colleagues showed the presence of nicotine and cotinine in the vaginal fluid of cigarette smokers. The uterine cervix of a smoker is thus bathed in the metabolic products of cigarette smoking, much like the epithelial lining of the urinary bladder, but at higher concentrations.

Based on these data, physicians must view cigarette smoking as an independent risk factor when making recommendations about the frequency of Pap smears and should recommend careful surveillance regardless of a woman's sexual exposures.

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Milk-Borne Diseases

SINCE THE ADVENT at the turn of the century of pasteurization of nearly all market milk in this country, large-scale outbreaks of milk-borne diseases have been rare. Where disease problems still occur, these have been primarily associated with raw (unpasteurized) milk and, on rare occasions, with pasteurized milk. A vivid example of this latter situation was documented in Chicago in the summer of 1984 and again in March and April 1985 when thousands of consumers of pasteurized low-fat milk produced by a single dairy were infected with *Salmonella typhimurium.* The findings suggest that the pasteurized milk was inadvertently mixed with raw milk. This underscores the documented hazard of raw milk as a source of human pathogens. Virtually all other episodes of disease problems associated with "pasteurized" milk have been found, ultimately, to be due to postpasteurization contamination or inadequate pasteurization.

Listeriosis is a disease that has been associated with pasteurized and, more recently, in the Jalisco cheese outbreak in California, with inadequately pasteurized or postpasteurized contaminated milk. A possible explanation as to why *Listeria* can still be a problem with pasteurized milk is that leucocytes (which are in milk, especially from infected cows) may contain and thereby protect *Listeria* organisms from inactivation by routine pasteurization procedures. Obviously, if some *Listeria* can persist despite routine pasteurization procedures, raw milk must pose an even greater risk from this bacterial pathogen.

The major disease problems associated with milk in this country, however, are those of salmonellosis and campylobacteriosis; these continue to be linked to raw milk, including certified raw milk. In addition, other diseases linked to raw-milk ingestion include brucellosis, colibacillosis, corynebacteriosis, staphylococcal poisoning, streptococcal infection and tuberculosis. A newly recognized problem that has been

linked to the consumption of raw milk is that of "Brainerd diarrhea," a type of diarrhea first reported from Minnesota in 1984. This illness is characterized by the abrupt onset of numerous watery stools (15 to 25 per day) and a pronounced urgency to defecate but few systemic symptoms. Cases of Brainerd diarrhea tend to be persistent and 70% of patients have continued to experience diarrhea a year or more after onset. No etiologic agent has yet been identified.

Health care providers need to be alert to the potential of milk-borne disease, especially when raw milk or raw milk products are consumed. More than 95% of all milk in this country is pasteurized, but more than 95% of all milk-borne outbreaks are due to raw milk.

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Combined Oral Contraceptives and Cancer

COMBINED ORAL CONTRACEPTIVES contain an estrogen and a progestogen in each pill taken during a monthly cycle of use. They were first introduced in the United States in 1960, and it has been estimated that as many as 70% of all women of reproductive age in this country have used these products. Because they are used by such a large number of healthy women with alternative methods to prevent unwanted pregnancies, much higher standards for their safety are warranted than for drugs that are used therapeutically by a smaller number of women with illnesses that result in morbidity or mortality if untreated. One area of major concern is whether combined oral contraceptives alter the risk of certain neoplasms, and many epidemiologic studies have been done to address this issue.

These studies are of two types. In prospective studies, of which there are four major ones, a large number of women using various methods of contraception are observed over a period of time and rates of various cancers in users of oral contraceptives are compared with rates in users of other contraceptive methods. In case-control studies, a series of cases of a particular cancer and a comparable disease-free control group are assembled and their prior use of steroid contraceptives contrasted. Scores of both retrospective and prospective studies have been conducted. Although no single study is definitive, and many questions remain unanswered, results from these investigations provide sufficient information to draw tentative conclusions regarding the influence of combined oral contraceptives, as they have been used in the past, on the risk of neoplasms of the breast, ovary, endometrium, cervix and liver.

At least eight studies have shown the risk of epithelial ovarian carcinomas to be reduced in women who have used combined oral contraceptives. The amount of protection increases with the number of years they are taken and may reach a reduction of more than 50% after five years of use. A similar protective effect has been observed for endometrial cancer. These protective effects appear to persist for a number of years after stopping their use.

Combined oral contraceptives have also been shown to reduce the risk for both benign cystic disease and fibroadenomas of the breast. They have not altered the risk of mammary carcinomas. More than a dozen case-control studies and three prospective studies have failed to convincingly show an increased risk in women who have ever used combined oral contraceptives, in long-term users or in women who used oral contraceptives a number of years in the past. The use of oral contraceptives by women at an early age or before their first pregnancy has been associated with an increased risk of breast cancer in some recent studies, but not in others, and this issue is currently a topic of active investigation.

Cervical cancer has been particularly difficult to study because in some cultures women who use oral contraceptives, like women who are at increased risk for this disease, tend to have multiple sexual partners, and it is difficult to separate the effects of this sexual behavior of oral contraceptive users on risk from the actual effect of the contraceptives. Detailed, accurate sexual histories are required, and these are difficult to obtain. Studies of cases of carcinoma in situ in relation to oral contraceptives have yielded inconsistent results, probably in part because the sexual behavior of the study subjects was not adequately considered. However, recent results from three prospective studies and one case-control study have shown an increase in the risk of invasive cervical cancer in users of combined oral contraceptives, suggesting that these products may enhance the progress of preexisting cervical lesions. Further investigations of this issue are under way. Although it cannot be concluded with certainty that oral contraceptives enhance the risk for invasive carcinoma of the cervix, users of these products, like other sexually active women, should have periodic Papanicolaou tests.

Hepatic cell adenomas are benign but highly vascular, can rupture and occasionally cause death. The risk of these tumors is increased in users of combined oral contraceptives, but fortunately this is an extremely rare phenomenon. There is no good evidence that the risk of hepatic cell carcinoma is increased by using oral contraceptives, although this is a topic currently under investigation.

Other neoplasms, including melanomas, pituitary adenomas and carcinomas of the thyroid and gallbladder, have been investigated, but oral contraceptives have not been shown to enhance their risk. Formal studies are continuing to provide the information needed to develop an accurate risk-benefit assessment of combined oral contraceptives. To date, they appear to be remarkably safe products and may prevent more cancers than they cause.

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The Lung Cancer Epidemic

PUBLIC HEALTH PROGRAMS were developed to solve serious community health problems, and epidemics have always been among the most pressing of those. In place of the vanished tuberculosis epidemic of the last century is the current lung cancer epidemic. This disease is not directly transmissible from one person to the next except insofar as smoking behavior, its major recognized causal agent, is a model for mimicry by one's companions.

Lung cancer deaths have now surpassed breast cancer deaths as the leading cancer mortality in women. This increase is unquestionably the result of an increasing proportion of the female population that smokes. This is particularly true and problematic with teenaged women.

Despite the protestations of the tobacco industry, cigarette smoking is recognized as the most important cause of lung cancer, though it acts as a tumor promoter rather than a tumor initiator. Stopping smoking has been shown to diminish the risk of lung cancer mortality as the period of abstinence lengthens after the first year.

In conjunction with smoking, workplace exposures to carcinogens (asbestos, bischloromethyl ether, chromates, nickel carbonyl and so forth) are important causes of lung cancer. Urban airborne pollutants also contribute to risk but to a much lesser degree. A sequel to the recent wave of home-insulation improvement has been the indoor accumulation of radon gas whose α-emitting daughter products are carcinogenic when inhaled. Though controversial, there is some suggestion that exposure to cigarette smoke may be involved in an increased lung cancer risk for a nonsmoker (passive smoking).

Although in some states the annual increase of cases of lung cancer seems to have peaked, the clearly excessive risks of lung cancer occurrence remain. More effective documentation and control of high-risk circumstances are needed to achieve significant levels of prevention. Each state needs to follow the US Surgeon General's lead, declare lung cancer to be an epidemic and allocate resources for epidemiologic surveillance and control. Prevention is the ultimate form of ethical medical cost control.

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Nonmedicinal Treatment of Hypertension

AS A RESULT of increased consumer awareness of the risks of hypertension and increased physician awareness of the benefits of early detection and treatment, primary care clinicians are more frequently encountering persons with mild hypertension (diastolic, 90 to 104 mm of mercury). Rather than immediately prescribing drugs, it may be preferable to negotiate with patients various life-style changes that have been shown to lower blood pressure. The possibility of avoiding medication is a strong incentive for many people, thereby increasing patient compliance.

The nonmedicinal approach to treating hypertension takes into account nutrition, weight, exercise and stress management.

Nutrition

Patients with hypertension need to be educated about avoiding salt and, more important, salty foods. Although we now know that not all persons are salt-sensitive, the excessively high average daily American intake of salt, combined with the lack of an accurate means of predicting who is salt-sensitive, justifies this recommendation for all patients with hypertension. Giving patients a handout listing the salt content of various foods saves physicians time and serves as a valuable reference for a patient. If hyperlipidemia is detected, then further nutritional counseling about avoiding high-cholesterol foods (organ and red meats, eggs, whole milk dairy products and shellfish) or high triglyceride foods (sugar, sweets and alcohol) with the help of additional patient handouts or a nutritionist referral would be necessary.

Weight

There is a direct correlation between obesity and hypertension. Although a goal is set to achieve and maintain a realistic body weight, it is surprising how even a small loss of 7 to 9 kg (15 to 20 lb) can lower a mildly elevated blood pressure to an acceptable level. The loss is best achieved slowly as the person adopts a more healthy diet rich in fiber and complex carbohydrates and low in fat and sugar and embarks on a regular exercise program.

Exercise

Daily sustained aerobic exercise results in lower blood pressure, lower serum levels of cholesterol and triglycerides, a slower resting heart rate indicative of a more efficient cardiovascular system, weight loss from both increased caloric expenditure and heightened metabolic rate and lowered stress levels. Recommending books like *Fit or Fat* by Covert Bailey provides a patient with guidelines for the length of time required for various aerobic activities and their desired maximum heart rates based on their general state of health.

Stress Management

Attempts to cope with today's highly technologic, impersonal and frustrating society have caused an elevated blood pressure in many people under high adrenergic stimulation. Because many people have difficulty identifying or acknowledging their stress, this aspect of nonmedical treatment of hypertension may require more in-depth discussion at subsequent visits. Nonetheless, a brief general discussion of how stress raises blood pressure, examples of various stress inducers (such as work, interpersonal relationships, finances) and a list of activities or techniques designed to lower stress are essential. A patient handout is again very helpful, listing such relaxing possibilities as hobbies, aerobic exercise, breathing exercises, biofeedback, meditation, music and reading, among others.

These four nonmedicinal treatments of hypertension should also be used with cases of moderate and severe hypertension. Obviously, people with higher blood pressures re-

quire medicinal treatment as well, but early emphasis by physicians about personal habits shows that a patient's life-style has contributed to his or her illness and that moderating harmful habits would greatly enhance the effect of medication, resulting in lowered doses, fewer side effects and cost containment, and give patients a sense of control over their own health.

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Diet and Cancer

DESPITE ADVANCES in treatment, age-adjusted mortality rates of cancer have continued to increase at a rate of about 3% every decade. Data on secular trends in incidence are less reliable, but it is probable that age-adjusted incidence rates are increasing at an even greater rate. Most of the increases can be attributed to cigarette smoking, but many cancers unrelated to smoking (such as colorectal cancer) remain as important causes of death. The number of deaths each year due to colorectal cancer (about 60,000) is second only to lung cancer (about 126,000), and it is the leading cause of cancer death in nonsmokers.

Diet appears to play a role in the risk of colorectal cancer. Burkitt's observation with Trowell, Cleave and others that Africans appeared to be at very low risk for colorectal cancer stimulated others to examine the effect of dietary fiber in case-control studies. Several such studies supported the idea that fiber might reduce the risk of colorectal cancer, whereas others were inconclusive. Graham in upstate New York observed that certain vegetables (broccoli, cabbage and brussels sprouts) were associated with a particularly low risk of colorectal cancer.

We suggested that vitamin D and calcium might reduce the risk of colorectal cancer, based on the strong geographical gradient for colorectal cancer in the United States and throughout the world. In particular, colorectal cancer seemed to occur much more frequently in places distant from the equator than in equatorial regions. This theory stimulated further investigation of the possible role of dietary vitamin D and calcium because a principal effect of latitude is increased synthesis in the skin of vitamin D from cholesterol and increased intestinal uptake of calcium.

In a recent study we examined the risk of colorectal cancer according to dietary intake of calcium and vitamin D in Chicago men. Because the men lived in a place where there is relatively little sunshine, well below the US median for solar energy from ultraviolet light at ground level per day, we speculated that dietary sources of vitamin D would be important.

The results of this study show that men who had the lowest intake of vitamin D and calcium had nearly three times the risk of colorectal cancer as men who had the highest intake. Men with intermediate intakes had an intermediate risk of colorectal cancer.

This finding can be added to the work of Shekelle, Bjelke and others showing a protective effect of the carotenes, vegetable-derived previtamin A, on the risk of lung cancer and that of Graham and others showing protective effects of citrus fruit on cancer of the upper gastrointestinal and respiratory tracts. Another study by Phillips showed a reduced risk of many varieties of cancer in association with a Seventh-Day-Adventist (vegetarian, nonsmoking, non-alcohol-drinking) life-style.

A diet to reduce the risk of cancer would include 2.5 to 3 glasses a day of nonfat milk (or 1,000 mg of calcium and 200 to 400 international units of vitamin D_3 per day for lactose-intolerant persons), yellow and green leafy vegetables at least once a day and citrus fruit or juice daily. Such a diet would also require moderation in the use of alcohol (two or fewer drinks, glasses of wine or bottles of beer per day). Restricting fat intake to no more than 20% to 30% of calories and including a bran muffin or the equivalent in dietary fiber every two days would likewise be prudent.

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Hyperlipidemia and Preventing Coronary Heart Disease

THE ASSOCIATION between hyperlipidemia, especially high low-density-lipoprotein cholesterol, and the incidence of coronary heart disease is a consistent finding in most, if not all, prospective population studies. Indeed, the observed association meets the established scientific criteria for causation and poses two important questions for clinicians. The first question is whether a blood cholesterol-lowering regimen should become a routine part of a practitioner's efforts at prevention. The second question, more strategic than conceptual, is what should be the target population for such a regimen?

Clinical trials on secondary prevention of coronary heart disease—that is, preventing death following acute myocardial infarction—have failed to show a beneficial effect of reducing the blood cholesterol level by dietary means, cholesterol-lowering drugs or both. Thus, in regard to secondary prevention of coronary heart disease, the first question cannot be answered in the affirmative. This makes the second question moot.

As for primary prevention—that is, preventing disease before it strikes—there is evidence that lowering blood cholesterol levels could be beneficial in some persons. Results of a recently completed trial in the Lipid Research Clinical Centers showed that the combination of a prudent dietary regimen and a cholesterol-lowering drug, such as cholestyramine, reduced the incidence of fatal and nonfatal coronary heart disease in men with average blood cholesterol levels of 260 mg per dl and above. Thus, the answer to the first question for primary prevention of coronary heart disease is a qualified

yes. This leaves the issue of the target population for prevention open for debate.

There are two models in practice for preventing coronary heart disease. One is a community model in which the target population is the total community. The desired program is aimed at the general population regardless of the level of risk among persons within that population. The other is a medical model of prevention in which the target population consists of persons at high risk who are identified in advance and the desired prevention program—that is, the blood cholesterol-lowering regimen—is targeted at them directly, under medical supervision.

The evidence on the efficacy of a cholesterol-lowering regimen for primary prevention of coronary heart disease is supportive, at best, of a prevention program only under a medical model. Physicians have a unique opportunity to primarily prevent coronary heart disease in their practices by identifying persons with high levels of blood cholesterol (260 mg per dl and above), especially when other risk factors such as hypertension, obesity and cigarette smoking are present, and intervening according to a medical model of prevention under their supervision.

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Preventing Falls in Elderly Persons

FALLS IN THE elderly are a prevalent cause of injuries and an important cause of morbidity and mortality. The cumulative yearly incidence of falls in elderly populations may be 30% to 40%, with 8% to 40% of falls resulting in fractures and 3% of falls resulting in hospital admission. Only half of the elderly patients admitted to hospital as a result of falls are alive one year later.

Primary prevention of falls includes removing hazards in the home. Standard environmental hazards are loose rugs, extension cords, slick bathtubs, stairs and poor lighting. Ambient temperature may be a hazard, as thin or undernourished elderly patients may fall due to lack of coordination resulting from hypothermia. Thin elderly women with hip fractures have lower body temperatures on admission to hospital than do well-nourished elderly women with hip fractures.

Secondary prevention of falls—that is, preventing their recurrence—depends partly on a clinical examination to search for reversible intrinsic causes. There is no validated screening protocol for falls available, and the differential diagnosis of falls is extensive. A prudent physician would search first for risk factors that merit treatment irrespective of their association with falls, such as visual problems, foot problems, drug toxicity, cardiac arrhythmias, seizure disorders and muscle weakness due to thyroid disease. Intervention to modify other risk factors, such as physical therapy for abnormal gait or a cane for abnormal balance, may be appropriate. At present, however, few data exist documenting the efficacy of risk-factor screening or modification in preventing falls.

More data have accumulated that falls are related to declining physical function. In one study, controlling for functional state eliminated the association of falls with age. In a study of predictors of falls in women with Alzheimer's disease who were in an institution, falls were more closely related to physical decline than mental decline. Hand strength, which correlates with overall body strength, is a predictor of falls and a predictor of complications from an operation for hip fracture. Muscle biopsies at the time of surgical procedure in patients with hip fractures show more leg muscle atrophy than is present in the general population.

A careful clinical examination of patients who fall seems reasonable. Due to the large number of causes for falls and the relationship of falls with physical function, a fall may be a sentinel event for the onset of a disease or of a decline in physical function. Presumably, interventions to prevent falls and to prevent further physical decline are more effective if initiated early. Exercise may have a role in the primary prevention of injury due to falls, as studies show that exercise in the elderly can maintain or increase bone mass as well as increase muscular strength and endurance.

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Disease Outbreaks in Day-Care Centers

THE INCREASING PROPORTION of mothers who are working has resulted in an increase in the number and importance of facilities where children can be cared for during the working day. These vary from neighbors who take care of as few as two to four children within their homes as licensed or unlicensed "day-care homes" to licensed day-care centers that take care of a few dozen to a few hundred children. The children may range in age from 3 months to kindergarten level.

Aggregating these children into a common area, with common playthings, provides an ideal opportunity for the spread of infectious agents by direct contact, by fomites and by airborne droplet nuclei. In addition, these children must be fed, either snacks or meals, from kitchens not usually staffed, equipped or designed for the level of food sanitation required for public eating places. Consequently, diseases spread by the fecal-oral route are frequent, especially when non-toilet-trained infants and toddlers are present. The disease of greatest significance is hepatitis A, which was found in one study to have an asymptomatic-to-symptomatic ratio of 22:1 among day-care children younger than 3 years, this in contrast to a ratio of 1:8 among the staff of a day-care facility. Clinical cases occurred in 88% of the households that had a child in the center. Outbreaks of diarrheal disease, especially shigellosis and giardiasis, have occurred frequently; during

the first five weeks of enrollment in a day-care center, there is an average diarrheal attack rate of 25%, declining to 10% among those remaining in the center. The spread of colds and fevers due to a wide variety of microorganisms is traditional; these are most frequent among younger children.

Some control measures are obvious. A program of washing the hands of the staff and of the children after possible contamination with fecal material can reduce the incidence of diarrheal disease by about half. A program of administering immunoglobulin when cases of diarrheal disease occurred in a center child or employee or among parents in two families eliminated cases among center personnel and reduced cases in the community by 75%. Rigorous adherence to immunization schedules eliminates the threat of the vaccine-preventable diseases. Day-care center operators or parents are concerned about keeping a sick child out of the centers. Because infectious agents have probably already been spread during the late incubation, however, exclusion may only force a parent to seek another place for child care, further spreading the infection. Therefore, consideration should be given to admitting sick children to the day-care center if facilities and personnel are available to permit separating sick from healthy children.

Day-care centers will increase in importance; professional supervision to assure minimal disease transmission is necessary.

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Editorials

On the Nationalization of DRG Payments

As this is written, it appears that the federal government is determined to move ahead with its plan to impose uniform national standards for the administration of its Medicare program. The diagnosis-related groups (DRGs) are already in place, and now the goal is to make the payments uniform nationwide to hospitals for these services. There has been remarkably little discussion as to whether this will even be workable, or of what might be the fallout in terms of patient care for the Medicare beneficiaries and others in various parts of the country. Nor has much thought been given to what might be the long-term effects of this particular federal initiative. It is already known that plans are being made by the government to include physicians' services in the DRG system, although little has been said so far about making the payments uniform nationwide to physicians for these services.

The DRG system is the most recent in a cascade of federal initiatives that have attempted to control or reduce the rising costs of health care. None of these has been very effective. Many were based on simplistic assumptions that proved to be false. The DRG system seems to have come into being more for the convenience of the government than any of its predecessors. Some kind of manageable national standards are probably essential, and certainly convenient, for the smooth and easy administration of a national program, particularly one that reaches as far into the infrastructure of society as does the Medicare program. But even so, it remains to be seen whether this will work any better than the earlier initiatives. It too may be based on a false assumption—in this case of a bureaucratic stereotype of a homogeneous nation and a homogeneous population. This we clearly do not have. It seems certain that national standards for Medicare payments will result in many inequities due to genuine regional differences, to say nothing of genuine differences in the needs of individual Medicare beneficiaries. It is not yet known to what extent these inevitable inequities will prove to be acceptable to society.

But for the long haul there may be an even more fundamental issue that has yet to surface. If payments for DRG services to Medicare patients are made uniform nationwide, then a segment of mainstream medicine will have effectively been nationalized. Are we really ready, as a nation, to move toward a single national system of mainstream health care, or would we prefer to retain our pluralistic system which allows for regional and individual variations and differences? Is there a chance that a bureaucratic imperative for administrative convenience at the national level might actually make this decision for us, even though no one may have planned it that way? It would seem that this just could happen.

To date, the only government initiative that has been really effective in controlling health care costs has been the systematic underfunding of government supported health care programs. The DRG system payments are now an obvious candidate for reduced funding, and this may be expected to occur as soon as it is clear that the program is a "success." Underfunding, whether in the public or private sector, is a powerful tool in health care today. In the final analysis, it produces de facto rationing of health care services. So far the poor have been getting the worst of it. Where the responsibility lies for deciding who gets what care is not yet clear. No one has yet stepped forward and claimed this responsibility. Elsewhere in this issue is a position statement, "On Rationing of Health Care," adopted by the Council of the California Medical Association. This at least places the issue on the table. Just as the bottom line in a financial statement shows the profit or loss, so the bottom line in health care will be the human profit and loss from de facto or planned rationing should this latter come about.

One can be uneasy about the nationalization of DRG payments. It is hard to see where this may lead, or in what way this federal initiative to cut costs will succeed, if indeed it does succeed.

MSMW

Cellular Basis for Injury and Repair in the Adult Respiratory Distress Syndrome

Therapy for the adult respiratory distress syndrome (ARDS) has continued to be supportive with an emphasis on mechanical ventilation, positive end-expiratory pressure (PEEP), careful management of intravenous fluid administration and therapy for the associated clinical disorder. Overall mortality from this disorder continues to be high, about 60%.[1] This dismal figure is not much different from the mortality figures available almost a decade ago when a National Institutes of Health Task Force on the Adult Respiratory Distress Syndrome recommended that intensive clinical and basic research be funded to increase our understanding of this devastating disease. Even though a better outcome has not yet been achieved, a number of clinical and experimental studies have advanced our knowledge of the syndrome.

Well-designed, prospective clinical studies have established that sepsis, aspiration of gastric contents and major trauma are the three most common clinical disorders associated with a high risk for the adult respiratory distress syndrome.[1] In addition, a controlled trial of prophylactic PEEP was completed recently in a group of patients at high risk for the development of ARDS.[2] Unfortunately, the results showed that applying 8 cm of water of PEEP before the development of acute respiratory failure did not prevent the occurrence of the disorder. Nevertheless, since the syndrome develops in most patients within 24 hours of the inciting clinical event,[2] it is important that these investigators were able to identify high-risk patients early enough in their clinical course so that treatment could be delivered before the onset of the fully developed syndrome. Similarly, the success of current and future clinical trials designed to test new treatment modalities will depend on identifying high-risk patients early in their clinical course. At our own institution, we have devel-

ABBREVIATIONS USED IN TEXT
ARDS = adult respiratory distress syndrome
PEEP = positive end-expiratory pressure

oped a scoring system to quantify the progression of acute respiratory failure in the early phase of respiratory failure before a full-blown adult respiratory distress syndrome develops.[3] Other clinical studies have determined that the syndrome frequently occurs in patients with multiorgan failure and is, of course, frequently complicated by infection.[4]

A number of experimental studies have provided new insights regarding the pathogenesis of the early phase of acute lung injury. We now know that one of the earliest abnormalities in ARDS is the development of a protein-rich pulmonary edema that is secondary to an increase in lung vascular permeability. Furthermore, the results of some experimental studies suggest that neutrophils play an important role in mediating the early phase of the increased lung vascular permeability.[5,6] Activated neutrophils that sequester in the pulmonary circulation can release toxic oxygen radicals, proteolytic enzymes and lipoxygenase products of the arachidonic acid cascade, all of which may in turn increase endothelial and epithelial permeability and provide additional chemotactic signals that amplify the inflammatory response.[7,8] Although neutrophils are important in some models of lung injury, the adult respiratory distress syndrome certainly does occur in neutropenic patients, and experimentally oxygen-induced lung injury does not depend on the presence of neutrophils.[9] Even though the clinical features of this syndrome are similar regardless of the associated clinical disorder, the precise mechanisms of lung injury may depend on whether the insult is delivered via the circulation (as in sepsis or fat embolism) or via the airways (as in aspiration of gastric contents or fresh water).

Even though considerable progress has been made in understanding the early phase of increased lung vascular permeability, we still know very little about the mechanisms responsible for persistent respiratory failure and the cellular and biochemical factors that regulate the process of lung repair. Further progress in unraveling the complex mechanisms of injury and repair will probably parallel advances in understanding the cell biology of both resident lung cells and circulating neutrophils and monocytes. Recently, for example, Ryan and co-workers have succeeded in culturing and studying endothelial cells from the pulmonary circulation. They and other investigators have learned that the endothelial barrier is not immunologically inert, and important endothelial-neutrophil interactions are being investigated.[10] In addition, a number of laboratories have evaluated the function of neutrophils and the factors that control their adherence, aggregation and activation in the pulmonary circulation.[10] Some investigators have focused their work on the alveolar macrophage, already known to be an important mediator of lung inflammation in chronic interstitial lung disease and now being studied for its role in modulating the inflammatory and the fibroblastic response in ARDS.[11]

From the standpoint of a cell biologist, the best understood of all the resident lung cells is probably the alveolar type II epithelial cell. In this issue of the journal, Mason, a cell biologist and a pulmonologist, provides a fresh perspective on the adult respiratory distress syndrome, emphasizing that recent insights into the function of alveolar type II cells may shed new light on the pathophysiology of ARDS and suggest new pharmacologic approaches for treatment. Under normal conditions, type II cells synthesize, secrete and reabsorb surface-active material, which is necessary for alveolar stability. In hyaline membrane disease of the preterm infant, surfactant deficiency is the critical factor in the pathogenesis of the infant respiratory distress syndrome. In fact, when Petty originally described the adult respiratory distress syndrome, his selection of the term ARDS was influenced by clinical and pathologic similarities between the infant and adult respiratory distress syndromes. Mason suggests that injury to type II cells in adult cases may result in production of an ineffective form of surfactant that may be responsible for some of the compliance and gas-exchange abnormalities after acute lung injury.

Is a deficiency of normal surfactant responsible for the observed pathophysiologic abnormalities of ARDS? The early phase of the disorder is characterized by a substantial decrease in static lung compliance, and it is possible that alterations in the production of surfactant from alveolar type II cells may contribute to alveolar instability, atelectasis and right to left intrapulmonary shunts. However, much of the decrease in lung compliance and the severe hypoxemia in the early phase of the syndrome can be accounted for by the pulmonary edema that fills the interstitium and air spaces of the lung. In addition, recent experimental studies have indicated that there are pronounced changes in airway resistance and lung compliance in sheep given *Escherichia coli* endotoxin even before extravascular lung water rises. These mechanical changes in the lung can be prevented with inhibitors of the cyclooxygenase pathway of prostaglandin metabolism.[12] Nevertheless, one group of investigators has reported that biochemically abnormal surfactant can be lavaged from patients with the adult respiratory distress syndrome, suggesting that the production of surfactant may be abnormal, possibly because of injury to type II cells.[13] In the subacute and chronic phases of the disorder, there is a notable decrease in lung compliance even though pathologic studies have shown that most of the edema has been cleared from the lung. In this chronic phase, deficiency of normal surfactant may be an important cause of the poor lung compliance, but this mechanism is difficult to separate from the changes in lung tissue compliance caused by the increase in fibroblastic activity and increased deposition of collagen that develops in the later phase of the disease.[14]

How important is the type II cell in recovery from acute lung injury? It has been shown pathologically that the type II cells are necessary for the reepithelialization of the alveolar barrier after an initial phase of acute lung injury results in destruction of type I alveolar epithelial cells.[14] There is some evidence that an intact basement membrane may be necessary for type II cells to provide a new alveolar epithelial barrier, but the precise biochemical signals by which this process is regulated have not been established.

Finally, there is new information that alveolar type II epithelial cells are capable of active ion transport from the mucosal to the serosal surface; this process can be inhibited by sodium-entry blockers, and it can be accelerated by β-adrenergic agonists (see article by Mason in this issue). Recent physiologic studies from our own laboratory have contributed

evidence that active transport of electrolytes may be important in clearing edema fluid from the air spaces of the normal sheep lung.[15] In addition, we have recently presented evidence that β-adrenergic therapy can augment alveolar liquid clearance in sheep.[16] Clearly, it is possible that type II epithelial cells may be important in removing alveolar edema, and it is also conceivable that injury to type II cells early in the course of the adult respiratory distress syndrome might result in a slower resolution of alveolar edema.

In summary, based on experimental and clinical studies, Mason is probably correct in postulating a major role for alveolar type II epithelial cells in both the evolution and resolution of this syndrome. It is also likely, however, that circulating neutrophils and monocytes that interact with resident cells of the lung (endothelial cells, alveolar macrophages and perhaps airway epithelial cells) are important in the pathogenesis as well as recovery from this syndrome.

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Wouldn't It Be Wonderful!

THE POSSIBILITY OF NUCLEAR WAR, nuclear terrorism or even nuclear accidents weighs heavily on the world today, and this will continue for the foreseeable future. The nuclear genie is out of its bottle and there is no longer any way to get it back in. If humanity is to thrive, or even to survive, ways must be found to accommodate the ever present reality of the dual threats—the possibility that nuclear force will be used to achieve someone's purpose or that purposeless nuclear accidents will occur with the accompanying though unwanted devastation.

As everyone knows, the nuclear arms race between the United States and the Soviet Union has been going on apace. It is generally conceded that both sides now have an ample supply of weapons—easily enough to destroy human civilization. Recently, with the ascent of Premier Gorbachev to power, the rhetoric from the Kremlin has changed and a unilateral moratorium on nuclear testing has been proclaimed. At this writing the rhetoric from Washington has not changed. It is obvious that everyone everywhere remains suspicious and skittish.

It is a fact that the arms race is a major economic drain on both the major powers. It is diverting resources from what both nations would like to be doing at home. It is also a fact that two very different ideologies are at odds, and that each would like to see its own prevail throughout the world. In one, state control is as absolute as possible, and this control is enforced by means of a police state. The belief is that the collective good of the state takes precedence over individual freedom. The other stands for democracy, individual freedom, with only sufficient government to protect the rights of all. Each ideology, in its own self interest, cannot afford to have the other become too dominant. And a third fact is that all of humanity, regardless of ideology, lives together on this planet, sometimes called Spaceship Earth, in which there is real and increasing human interdependence—biologic, technologic, ecologic, social, economic and political.

These facts are the realities to be dealt with. The approach is and has been competition between and among autonomous and independent entities, with huge amounts of resources going into the competition. As far as nuclear weapons are concerned there will be no winners. It seems inevitable that the facts and realities just described will sooner or later lead to a more cooperative approach among autonomous and independent persons, groups of persons, human institutions, governments and nations. As the reality of autonomy is better recognized there will be less tendency to impose one's will or ideology upon others, with some reduction in the root causes of conflict. Perhaps, if the door is even slightly open, there could be a cautious approach at the highest levels to an international philosophy of "live and let live," and more specifically toward agreement and trust that could lead to some gradual curtailment of nuclear weapons. We should beware of moving too rapidly. Neville Chamberlain thought he had negotiated "peace for our time" just before World War II broke out. But it is time for greater worldwide recognition that the rules of the game are going to have to change, and that cooperation rather than competition will have to be the way of the future. The realities of nuclear power, independent ideologies and human interdependence, and the corollary, the need to develop instruments of cooperation, should be recognized and encouraged at many levels of human interaction.

A new era of genuine cooperation! Wouldn't it be wonderful!

MSMW

Subliminal Note: Could there be a message here for medicine?

Aging and the Thyroid

As a result of the medical advances that have occurred since the 2nd World War, we are living longer; 11% of the US population or approximately 25,000,000 people are aged 65 years or older. Moreover, this group represents the most rapidly growing segment of the population. This phenomenon, the potential impact of which was only recently appreciated, has brought about the current explosion of interest in the effects of the aging process, from middle life through senescence, on organ physiology and cell function and on the clinical and laboratory presentation of disease. As a result, a rapidly expanding information base is emerging and nowhere is this more evident than in the case of the endocrine system.

The aging process may affect hormone physiology in one or more of several ways depending upon the specific endocrine organ in question. First, it could lead to a primary alteration in the metabolic disposition of hormone which through regulatory mechanisms would lead to a secondary parallel alteration in production; if the setpoint for feedback regulatory control were not altered, plasma hormone concentration would remain unchanged. Second, the aging process could be associated with a primary alteration in hormone production rate, with the expected parallel alteration in plasma hormone concentration. Finally, it could be associated with alterations in tissue responsiveness to hormone. In the case of the thyroid hormones, some of these alterations appear to be operative in elderly persons. Several studies have shown a decrease in the metabolic clearance rate of L-thyroxine (T_4).[1,2] This is in all likelihood due to a primary reduction in the metabolic disposition of hormone which parallels the age-related reduction in lean body mass, rather than to an increase in plasma binding since thyroxine-binding globulin is essentially unchanged. Because plasma T_4 concentration remains unchanged,[3-5] the production rate of T_4, which is due entirely to glandular secretion, must be reduced. In the case of L-triiodothyronine (T_3), the situation is complicated by the fact that this hormone is derived in large part from the outer ring (5′-)monodeiodination of T_4 in the peripheral tissues and from glandular secretion.

The plasma concentration of T_3 in elderly persons has been a subject of some controversy. Early studies had suggested a substantial decrease with aging. In these early studies, however, the effects of concurrent illness, reduced caloric intake and medication—factors that are now known to profoundly influence T_3 production or disposition—were not considered. More recent studies conducted in healthy, ambulant elderly persons have shown a small decline in plasma T_3 concentration, but not of the magnitude that was initially suggested.[3-5] Since the metabolic clearance rate of T_3 is not increased in the elderly, this decline must reflect a decrease in the production rate of T_3. Because about 80% of T_3 production is derived from the peripheral monodeiodination of T_4, the decreased production rate may merely reflect the reduction in the overall metabolic disposition of T_4 cited above. If this were the case, the concentration of reverse triiodothyronine (rT_3), the alternate metabolically inert product generated through inner ring (5-)monodeiodination of T_4, would be expected to be reduced to a proportionately equivalent extent. This, however, is not the case; plasma rT_3 concentration does not decline as a function of age.[4,5] This observation suggests

ABBREVIATIONS USED IN TEXT

rT_3 = reverse triiodothyronine
T_3 = L-triiodothyronine
T_4 = L-thyroxine

that in addition to the quantitative alterations described above, there may also exist an age-related qualitative alteration in which iodothyronine outer ring deiodination (5′-deiodination) is selectively depressed. This would result in both reduced generation of T_3 from T_4 and reduced degradation of rT_3. On the other hand, the small decrease in plasma T_3 concentration could be due, at least in part, to a decrease in the contribution of glandular secretion to T_3 production. Although thyroid radioiodine uptake values fall within the normal range in elderly persons, the thyroid iodide clearance rate is reduced. However, to my knowledge, there are no data concerning the influence of the aging process on T_4-T_3 concentration ratios in thyroglobulin or in the thyroid venous effluent.

The acquisition of information concerning the influence of the aging process on neuroendocrine regulatory mechanisms has not kept pace with that dealing with peripheral hormone metabolism. With the advent of ultrasensitive radioimmunoassays for pituitary hormones and the development of releasing-factor stimulation tests, however, information in this area is emerging rapidly. Basal values of plasma thyroid-stimulating hormone in elderly persons are within the normal range for young adults, although in some cross-sectional studies the mean values tend to be somewhat higher than those in younger persons.[3,5] Responsiveness of the thyroid-stimulating hormone secretory mechanism to thyrotropin-releasing hormone, however, may be dampened, and this appears to be more prominent in elderly men.[6,7]

From the foregoing, it is evident that the aging process is accompanied by only subtle changes in the values of the standard thyroid function tests. Moreover, so far as is known, the values deviate from the norm in the expected manner when thyroid dysfunction supervenes. Thus, on purely theoretical grounds, thyroid diagnosis ought not to pose a problem in elderly persons. Unfortunately, in the clinical setting, this is not necessarily the case.

In this issue of the journal, Rosenthal and Sanchez survey the problem of thyroid diagnosis in the elderly. Two phenomena, in the main, contribute to this problem. First, the clinical presentation of thyroid dysfunction in elderly persons frequently differs from that in younger patients. For example, thyrotoxicosis may masquerade as proximal myopathy, as cardiac insufficiency, supraventricular tachydysrhythmia, or a worsening of anginal pattern, or as unexplained weight loss; often, the usual clinical manifestations that one associates with thyrotoxicosis in a younger patient are lacking, and goiter may be absent. Moreover, when some other severe illness coexists, the serum T_3 and T_4 concentrations may not display their expected increases. Consequently, the correct diagnosis is often delayed and presumably on occasion never made. In my experience, this is by far the commonest type of "missed thyroid diagnosis." The other phenomenon that may contribute to the problem of thyroid diagnosis is the presence of a systemic nonthyroid illness. An elderly patient may superficially resemble a patient with hypothyroidism in dis-

playing some hair loss, dryness of the skin and general slowing. When these changes are associated with the laboratory abnormalities of the "euthyroid sick syndrome," a mistaken diagnosis of hypothyroidism could be made and treatment instituted with potentially disastrous consequences. This represents the commonest form of thyroid "overdiagnosis." Rosenthal and Sanchez address this aspect in some detail and provide some guidelines for the laboratory diagnosis of hypothyroidism in a case of nonthyroid illness.

As alluded to above, aging is accompanied by some physical changes that are reminiscent of those of hypothyroidism. Accordingly, it has been suggested that the aging process after middle life may be due in part to reduced responsiveness of the tissues to thyroid hormones. In keeping with this suggestion is a recent observation that nuclear T_3 receptor affinity and density are reduced in mononuclear cells harvested from elderly persons.[8] However, it is difficult to reconcile this observation with the finding that the basal metabolic rate, the only index of thyroid hormone action that has been assessed in relation to age in humans, is appropriate for the mass of metabolically active tissue in elderly persons.[9] Moreover, lean body mass has been a more accurate predictor of thyroid hormone requirements than age.[10] Thus, the balance of evidence in humans to date would not support a role for reduced tissue responsiveness to thyroid hormones in the aging process.

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Case Reports

Altitude-Related Splenic Infarction in Sickle Cell Trait—Case Reports of a Father and Son

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SPLENIC INFARCTION and rupture associated with sickle cell trait and altitude have been reported in a limited number of well-documented cases. Many of the early studies did not record the actual presence of sickle cell trait by hemoglobin electrophoresis. Other disorders such as hemoglobin (Hb) SC disease may have accounted for the splenic infarction.

We report here the cases of two white male patients, a father and son, having sickle cell trait proved by hemoglobin electrophoresis, associated with splenic infarction and occurring on traveling from a low to a medium altitude.* Features of this disease in nonblacks are discussed along with a brief review of the literature.

Reports of Cases

Case 1

Patient 1, an 18-year-old white male diesel mechanic, had left his sea level home in Texas for a 36-hour bus trip to Santa Fe, New Mexico (2,134 m [7,000 ft]), to attend a religious retreat. About two hours before arriving in Santa Fe, at Clines Corners, New Mexico (2,195 m [7,200 ft]), he noted the onset of nausea and sharp upper left quadrant pain that prevented him from breathing deeply.

On physical examination he was well developed and appeared well nourished, his blood pressure was 120/80 mm of mercury and his pulse rate was 80 beats per minute. There was tenderness in the left upper quadrant of the abdomen and rebound tenderness was referred to that area. There was no organomegaly. Bowel sounds were diminished.

His hematocrit was 37%. The leukocyte count was 19,300 per μl with a normal differential cell count. A serum amylase level and results of an SMA-12 panel, urinalysis, an electrocardiogram and x-ray films of the chest and kidneys, ureters and bladder were within normal limits. Arterial blood gas determinations made while the patient was breathing room air were as follows: pH 7.42, partial oxygen pressure (Po_2) 58.3 mm of mercury, partial carbon dioxide pressure (Pco_2) 33.0 mm of mercury, bicarbonate 22.6 mEq per liter and arterial oxygen saturation (Sao_2) 93.7% (all normal for this altitude).

During the next three days physical findings localized to the left upper quadrant. His hematocrit dropped to 31%, a gastrointestinal series showed gastritis and duodenitis and a splenic scan showed no splenic visualization. The findings on ultrasound examination were consistent with a necrotic spleen and an abdominal angiogram showed complete occlusion of the splenic artery.

At that time sickle hemoglobinopathy was suspected and quantitative hemoglobin electrophoresis was done that showed the following pattern: Hb A_1 51.4%, Hb A_2 2.8% and Hb S 45.8%.

A splenectomy was done three days after admission. The spleen was enlarged and grossly infarcted. Microscopic examination showed multiple splenic infarctions with congestion. The splenic erythrocyte morphology was consistent with sickle cell hemoglobinopathy, although it was impossible to tell whether the sickling occurred in vivo or after the tissue was removed (Figure 1). No vascular abnormalities were noted during the operation or in gross or histologic examination of tissue specimens.

The postoperative course was uncomplicated except for a small amount of left pleural effusion that resolved spontaneously. A transfusion of two units of packed cells raised the hematocrit from a postoperative low of 28.7% to 32.5%.

He received nasal oxygen at 3 liters per minute during the postoperative period, which lasted 11 days. He returned home by automobile with instructions to use oxygen at 3 liters per minute until he reached an altitude below 610 m (2,000 ft), to prevent further sickling.

Case 2

Patient 2, the father of patient 1, was a 37-year-old white man who also lived in Texas at sea level. When he heard that his son was seriously ill, he left for Santa Fe by automobile and arrived 24 hours later, the day after his son's operation. About three hours after his arrival, he noted a right upper quadrant abdominal pain that soon moved to the left upper quadrant. He also noted dizziness and shortness of breath with minimal exertion. He had had similar symptoms during a recent vacation at 1,117 m (3,664 ft).

On examination he was well developed and in no acute distress. His blood pressure was 120/80 mm of mercury and temperature was 36.5°C (97.7°F). There was no abdominal tenderness, palpable masses or organomegaly. Bowel sounds were normal.

The leukocyte count was 12,700 per μl with a left shift. The total serum bilirubin level was 2.1 mg per dl with a direct fraction of 0.2 mg per dl. The lactic dehydrogenase level was

*We define low altitude as below 915 m (3,000 ft), medium altitude as 915 to 2,134 m (7,000 ft) and high altitude as above 2,134 m.

(Goldberg NM, Dorman JP, Riley CA, et al: Altitude-related splenic infarction in sickle cell trait—Case reports of a father and son. West J Med 1985 Nov; 143:670-672)

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ABBREVIATIONS USED IN TEXT

Hb = hemoglobin
Pco_2 = partial carbon dioxide pressure
Po_2 = partial oxygen pressure
Sao_2 = arterial oxygen saturation

elevated at 302 IU per liter. Results of an SMA-12 panel and an electrocardiogram and chest x-ray film were normal. An intravenous pyelogram showed normal renal function and anatomy but splenic enlargement was noted. Arterial blood gases were not measured with the patient breathing room air but while receiving oxygen nasally at 3 liters per minute, the values were as follows: pH 7.42, Po_2 76.2 mm of mercury, Pco_2 26.0 mm of mercury, bicarbonate 16.2 mEq per liter and Sao_2 94.8%.

A barium enema study the day after admission showed displacement of the splenic flexure by an extrinsic defect. The leukocyte count had increased to 17,000 per μl and the hematocrit had dropped to 32.8% from the admission value of 38.6%.

The pain steadily increased and the diagnosis of splenic infarction due to sickle cell trait had been confirmed in his son. Thus, a liver-spleen scan was done; the results suggested infarction, rupture of the spleen or both. A peritoneal lavage returned grossly bloody fluid.

Quantitative hemoglobin electrophoresis showed the following pattern: Hb A_1 55%, Hb A_2 3.4%, Hb S 41% and Hb CA_1 0.6%.

A splenectomy was done the day after admission. The spleen was infarcted and the splenic hilum and lower pole spontaneously ruptured. On microscopic examination there were large areas of infarction. The remaining preserved parenchyma contained greatly congested sinuses filled with abnormally shaped erythrocytes that appeared sickled. The appearance was very similar to the changes seen in his son's spleen. No vascular abnormalities were noted during the operation or in gross or histologic examination of the specimen.

His postoperative course was uncomplicated. He was discharged from the hospital on the seventh postoperative day with instructions to use nasal oxygen at 3 liters per minute until he reached his home at sea level.

According to the patient, miscegenation in his progenitors was likely.

Discussion

Sickle cell trait with splenic infarction at higher elevations was first reported by Smith and Conley[1] in 1955. They reported on 15 patients with splenic infarction occurring during high-altitude military flights. Eleven of the patients were shown by hemoglobin electrophoresis to have Hb AS. Splenic infarction was proved in the six patients who underwent splenectomy.

Failure to consider sickle cell trait in our patients, although admittedly unusual in nonblacks, led to the delay in diagnosis. McGrew, in screening naval recruits, found an incidence of 8% for the sickle cell trait in black recruits but of only 0.046% in nonblack recruits.[2,3] One fourth of the nonblacks were of Mediterranean origin, one of European and English origin and the remainder did not know their origin. Castro and Finch have suggested that nonblacks with sickle cell trait may be more susceptible to splenic infarction than blacks.[4] In a brief review of the literature, they found that 5 of 19 cases of splenic infarction in electrophoretically proved sickle cell trait occurred in whites.

The percentage of Hb S is a possible predisposing factor to splenic infarction. Jones and co-workers used this as a possible explanation for sudden death in four patients having sickle cell trait.[5] Only a third of patients with sickle cell trait have greater than 40% Hb S. Rotter and colleagues observed a high (42% to 44%) percent of Hb S in their patients who had sickle cell trait and splenic infarction.[6] This agrees well with the finding of 41% of Hb S in patient 2 and 45% of Hb S in patient 1. Lane and Githens, however, suggest that the level of Hb S has no significance.[7] Other predisposing factors such as the presence of Hb AC and sickle/thalassemia were not found in our patients.[8-10] Splenic infarction in blacks having

Figure 1.—Photomicrograph of splenic parenchyma from patient 1 showing numerous sickled cells. The specimen from patient 2 showed identical findings. (Reduced from magnification × 1,000.)

the Hb AS pattern who travel at medium to high altitudes has an incidence of less than 1%.[11]

Autosplenectomy early in childhood probably protects Hb SS patients against splenic infarction at high altitudes or during air travel.[11] We could find only two reported cases of altitude-associated splenic infarction in a patient with Hb SS. The patients were a 9-year-old black boy traveling in the Colorado mountains above 2,000 m (6,560 ft)[11] and a Saudi Arabian man traveling by commercial airplane.[12]

Exposure to altitudes as low as sea level has been associated with splenic infarction in patients having the sickle cell trait. O'Brien and associates reported a case of a white man of Sicilian descent who had an Hb AS pattern.[13] He had a splenic infarction, documented by technetium scanning, after climbing Mt Washington in New Hampshire. A similar case was reported from Ecuador.[14] A 58-year-old Mexican man with the Hb AS pattern who lived at sea level and said he had not excessively exerted himself had a splenectomy for splenic infarction.[15] Patient 2 in this report also had symptoms suggestive of splenic infarction while visiting at a relatively low altitude (1,118 m [3,668 ft]) several weeks before arriving in Santa Fe.

The maximum cabin pressure differential of 455 mm of mercury in a modern commercial aircraft makes it possible to maintain a sea level cabin pressure to an altitude of 6,860 m (22,500 ft). Higher flight levels might result in dangerous cabin pressures for a person having sickled hemoglobin.[16]

We found one case, reported by Claster and co-workers, of splenic infarction occurring in a person having sickle cell disease while flying in a pressurized commercial aircraft, although painful episodes do occur.[12] Green and associates recommended that patients with the sickle cell trait use oxygen continuously at standard cruising altitudes in pressurized cabins; they should not fly at all in unpressurized aircraft.[17] On the other hand, Mahony and Githens reported no instances of splenic infarction in black persons with Hb SS or Hb AS while flying in pressurized aircraft.[11] Although 20% of black persons with Hb SC and sickle/thalassemia had vaso-occlusive crises while flying in pressurized aircraft, only one (Hb SC) had a splenic infarction. They conclude that the danger of flying in a pressurized aircraft is very low.

In both of our patients, despite a lack of undue exertion, symptoms of splenic infarction developed from relative hypoxemia at medium altitudes, emphasizing that this syndrome can occur in white as well as black persons who have sickle cell trait while living and traveling even at sea level at rest. Thus, splenic infarction due to sickle cell trait must be considered in any patient presenting with upper abdominal pain at any altitude.

Families of such patients should be studied for and counseled about the sickle cell trait and disease and told to seek medical care if abdominal distress occurs under any circumstance. Perhaps, if the diagnosis were made early enough, the patient could then be treated with hydration, transfused with erythrocytes, transferred to a lower altitude or given oxygen before splenectomy became mandatory.[12,18]

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Acquired Heparinlike Anticoagulant in a Patient With Metastatic Breast Carcinoma

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NEOPLASTIC DISEASE is infrequently associated with the development of circulating inhibitors of coagulation. The most commonly described inhibitors include the lupus anticoagulant[1] or specific antibodies to factor VIII or other coagulation factors.[2,3] Only in the past few years has another type of inhibitor been reported, the heparinlike or "heparinoid" inhibitor. Three previous cases have been described[4-6] in which the occurrence of heparinlike inhibitors was associated with malignant hematologic disorders (leukemia or plasma cell dyscrasias). In two of these three cases, the patients had substantial hemorrhage and died as a result of inhibitor-associated bleeding.[5,6] We report the first case of a heparinlike inhibitor occurring in a patient with disseminated breast carcinoma; this inhibitor was associated with major bleeding that led to the patient's death.

(Rodgers GM, Corash L: Acquired heparinlike anticoagulant in a patient with metastatic breast carcinoma. West J Med 1985 Nov; 143:672-675)

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Report of a Case

The patient, a 42-year-old woman, presented in March 1980 with a breast mass. A biopsy specimen showed infiltrating ductal carcinoma, and a mastectomy was carried out. There was no personal or family history of bleeding. The patient had had a tubal ligation in 1972 without bleeding. At the time of mastectomy, 6/24 axillary nodes were positive for malignancy; the tumor was weakly positive for estrogen receptors. A bone scan showed no abnormalities. Postoperatively she received adjuvant chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil). She did well until January 1982, when back pain developed. After a repeat evaluation showed multiple bone and liver metastases, therapy with tamoxifen citrate was begun, as well as doxorubicin (adriamycin) hydrochloride and vincristine sulfate. There was no objective response to therapy and she had increased back pain and hypercalcemia. She was admitted to hospital for palliative radiotherapy.

On admission she was noted to have prolonged partial thromboplastin times (74 to 101 seconds; normal range, 23 to 38 seconds) and normal values for prothrombin time and fibrinogen. Fibrin-degradation products were consistently 20 μg per ml or less, and protamine sulfate (fibrin monomer) test was negative. The patient's thrombin times were repeatedly longer than 120 seconds and corrected to normal with toluidine blue. Results of an inhibitor screen (mixing test) using the thrombin time were positive at both 0 and 60 minutes of incubation (Table 1). With the exception of an admission platelet count of 38,000 per μl (a result of anthracycline administration nine days previously), all platelet counts were greater than 100,000 per μl.

Associated with the presence of the inhibitor, epistaxis and mild bruising developed. Further evaluation of the coagulopathy showed that factor VIIIc activity was 141% of normal; the reptilase time was normal. Although the laboratory values were persistently abnormal, the bleeding diminished and the patient was allowed to go home because no further therapy could be offered for her refractory, disseminated disease. Her hematocrit at discharge was 32%. One day after discharge she became dizzy and experienced syncope; her blood pressure at readmission was 80/40 mm of mercury and on physical examination she had widespread ecchymoses and a tense abdomen. She became progressively hypotensive, her abdomen became massively distended and she died within six hours of admission. Her hematocrit at readmission was 15%. An autopsy was not done.

Materials and Methods

Electrophoretic analysis of the patient's anticoagulant and reference glycosaminoglycan standards was done using the technique described by Horner.[7] Agarose gels (0.6%) were cast on Gel Bond film (Marine Colloids, Rockland, Maine) and electrophoresis was done using 0.87 mol per liter of acetate buffer, pH 3.0.[7] Specimens of plasma from the patient and a normal subject were treated with trichloroacetic acid (TCA) (final concentration, 10%). Reference glycosaminoglycan standards (heparan sulfate, keratan sulfate and chondroitin-4-sulfate) were prepared by J. A. Cifonelli, PhD. Hyaluronic acid from human umbilical cord and heparin from porcine intestinal mucosa (168 units per mg) were supplied by Sigma Chemical Co (St Louis, Missouri).

Results

A limited amount of plasma was available for analysis. By using the thrombin time to determine characteristics of the inhibitor, we found that the inhibitor was heat-stable (resistant to boiling for three minutes) and that its activity was neutralized by protamine. In additional experiments using the thrombin time and a heparin standard, the patient's plasma was found to have the equivalent of 1.2 units per ml of heparin activity. To further establish the heparinlike identity of the inhibitor, a partially purified heparinase prepared from *Flavobacterium heparinum* (provided by Peter Hovingh, MS, and Alfred Linker, PhD, University of Utah, Salt Lake City) was mixed with the patient's plasma and incubated. As shown in Table 2, incubation of heparinase with the inhibitor-containing plasma resulted in nearly complete correction of the prolonged thrombin time, supporting the previous finding that this patient's inhibitor was heparinlike.

To further investigate the nature of the patient's anticoagulant, electrophoresis of the anticoagulant and reference glycosaminoglycans was done using a previously described agarose gel technique.[7] Trichloroacetic acid was added to the patient's plasma (final concentration, 10%) to precipitate protein. The soluble fraction was neutralized, then analyzed by agarose electrophoresis. The use of dilute agarose permits electrophoretic separation of glycosaminoglycans based solely on differences in charge density.

Figure 1 shows the results of an agarose gel of glycosaminoglycan standards and TCA-soluble material from the patient's plasma and from a normal donor. Similar mobilities for these standards have been previously reported.[4,7] The acid-soluble material present in the patient's plasma (lane 5) had electrophoretic mobility that was substantially different from that of heparin and heparan sulfate but similar to that of hyaluronic acid (lane 8). The hyaluronic acid standard stained faintly and has been identified with an arrow. No similar acid-soluble material was detected in normal plasma (lane 6).

TABLE 1.—*Inhibitor Screen of the Patient's Plasma in a Thrombin Time Assay**

Specimen	Clotting Time (sec) 0 min	60 min
Patient plasma	>120	>120
Normal plasma	27.0	30.8
Patient plasma plus normal plasma	104.3	123.1

*Each specimen of plasma was incubated at 37°C. After incubation, the specimens were tested for inhibitory activity using the thrombin time. Each value represents the average of duplicate measurements.

TABLE 2:—*Correction of the Inhibitory Activity With Heparinase**

Specimen	Clotting Time, sec
Normal plasma + buffer	29.7
Normal plasma + heparinase	31.5
Patient plasma + buffer	50.4
Patient plasma + heparinase	36.3

*Each specimen of plasma was incubated with either buffer (150 mmol per liter of sodium chloride, 20 mmol per liter of tris[hydroxymethyl]aminomethane hydrochloride, pH 7.4) or with an equal volume of heparinase (1 mg per ml in buffer) for 3 h at 37°C. After incubation, the specimens were tested for inhibitory activity using the thrombin time value as the measure. Each value represents the average of duplicate measurements.

Discussion

Malignancy may be associated with the acquisition of various types of inhibitors of coagulation. These include fibrin-degradation products and paraproteins, which inhibit fibrin polymerization and impair platelet function; dysfibrinogenemias, which impede fibrin monomer polymerization or cross-linking, and specific antibodies to coagulation factors.[8] While many of these types of inhibitors may be associated with bleeding, the lupus anticoagulant, which can be seen with a variety of neoplastic diseases, is only rarely a cause of hemorrhage.[1] Recently, a new type of acquired anticoagulant has been described in patients with malignant hematologic disorders. Khoory and colleagues reported that in a patient with IgA myeloma an inhibitor developed that was characterized as a heparan sulfate proteoglycan.[4] This patient experienced pronounced soft-tissue bleeding. A report by Palmer and co-workers described a patient with IgG plasma cell leukemia who had significant visceral hemorrhage that resulted in death.[5] These authors concluded that their patient's inhibitor was a large-molecular-weight heparinlike molecule. Most recently, Bussel and associates identified a heparinlike anticoagulant in a young patient with acute monoblastic leukemia.[6] Visceral hemorrhage occurred and resulted in death.[6]

In all three of these cases, the underlying malignant diseases were hematologic-plasma cell dyscrasias or leukemia. In contrast, the present case was associated with metastatic breast carcinoma. In all four cases, the most sensitive test of the coagulopathy was the thrombin time assay. In all cases the thrombin time assay showed that positively charged agents such as protamine or toluidine blue neutralized the inhibitory activity, whereas reptilase times were normal. These findings are characteristic of the use of heparin, although no patient received heparin. Additionally, there was no strong evidence of disseminated intravascular coagulation: three of the four patients died of hemorrhagic complications.

Figure 1.—Electrophoresis of patient's anticoagulant and reference glycosaminoglycan standards in 0.6% agarose gel using 0.87 M acetate buffer, pH 3.0. Lane 1, amaranth (tracking dye); lane 2, heparin (50 μg); lane 3, heparan sulfate (50 μg); lane 4, keratan sulfate (50 μg); lane 5, patient plasma (trichloroacetic acid [TCA]-soluble material derived from 0.5 ml of original plasma); lane 6, normal plasma (TCA-soluble material derived from 0.5 ml original plasma); lane 7, chondroitin-4-sulfate (50 μg); lane 8, hyaluronic acid (50 μg) **(arrow)**; and lane 9, patient plasma (as in lane 5) plus heparin (25 μg). Conditions for agarose electrophoresis were similar to those previously described by Horner.[7] The direction of migration is from top to bottom.

Although the anticoagulant from our patient's plasma had functional similarities to heparin, its electrophoretic mobility was distinct from that of heparin or heparan sulfate (Figure 1). The mobility pattern also differed from that of the other heparinlike inhibitors that have been characterized by electrophoresis.[4,5] Mobility of the patient's anticoagulant was similar to that of hyaluronic acid, although the hyaluronic acid standard appeared to be more polydisperse than the patient's anticoagulant. Despite the similarity in mobility to hyaluronic acid, previous studies indicate that hyaluronic acid has minimal anticoagulant properties for this glycosaminoglycan.[9] It is possible that this patient's inhibitor may be a modified hyaluronic acid produced by the neoplastic process.

One interesting feature of these cases is the possible source of the heparinlike inhibitor. In the report by Khoory and colleagues,[4] short-term culture of the patient's myeloma cells did not generate the inhibitor, nor did extracts of the cultured cells show activity. Similarly, Bussell and co-workers[6] were unable to find inhibitory activity in extracts from their patient's monoblasts. Both of these reports suggested that the inhibitor may have come from the patient's blood vessels because heparin and related compounds (heparan sulfate proteoglycans) have been described as constitutents of the surface of the vascular endothelial cell.[10] Malignant disease may induce greater production or release of these substances, or both, or there may be disease-related vascular damage that releases the inhibitor.[4,6]

Another possibility is that the heparinlike inhibitor represents a normal embryonic or fetal substance, which in an adult is reexpressed in certain malignant disorders. Different malignant conditions may express various heparinlike inhibitors. This hypothesis is based on finding a heparinlike substance in the blood of normal newborns, but not in older patients.[11] Because several other markers of malignancy originally thought to be specific for neoplasia (α-fetoprotein,[12] Auer rods[13]) have subsequently been shown to occur in normal fetal or embryonic tissues, heparinlike inhibitors may also be members of this group of markers. An analogous situation exists with another group of inhibitors—the dysfibrinogens. It has been reported that the abnormal fibrinogens seen with hepatomas are structurally similar to fetal fibrinogen.[14]

As in the present case, in the previously reported cases no specific therapeutic intervention was attempted to correct the coagulopathy, as those patients with severe bleeding had progressive, refractory disease. However, based on the in vitro neutralization of heparin activity by protamine, one therapeutic possibility would be parenteral infusion of protamine sulfate. The thrombin time could be used to titrate subsequent doses, as has been suggested.[5,6]

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Renal Angiomyolipoma and Massive Retroperitoneal Hemorrhage During Pregnancy

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MASSIVE RETROPERITONEAL HEMORRHAGE due to spontaneous rupture of a renal angiomyolipoma is a rare complication of this unusual tumor. The association of this complication with pregnancy has been reported sporadically in the literature.[1-5] The importance of considering this possibility in the differential diagnosis of retroperitoneal bleeding during pregnancy has prompted this communication. During the past ten years we have encountered three cases of massive retroperitoneal hemorrhage resulting from rupture of a renal angiomyolipoma during pregnancy. In addition to reports of the three cases, we have included brief comments on the pathophysiology and diagnosis of this unusual tumor.

Reports of Cases

Case 1

The patient, a 29-year-old gravida 3, para 2 woman with known tuberous sclerosis, was seen in the 38th week of her pregnancy because of the sudden onset of severe left flank pain, orthostatic hypotension and a falling hematocrit. A plain abdominal roentgenogram showed a large left renal mass. A healthy male infant was delivered by cesarean section and on exploring the left retroperitoneal space, a large hematoma and a necrotic renal tumor with active bleeding were found. The kidney was removed and the patient made an uneventful recovery. Pathologic examination of a tumor specimen showed an angiomyolipoma. Postoperatively, a right renal arteriogram showed several small renal tumors consistent with angiomyolipoma.

Case 2

The patient, a 16-year-old mentally retarded gravida 1, para 0 woman with a previous diagnosis of tuberous sclerosis, presented during the 20th week of her pregnancy with hematuria of two days' duration. On admission to hospital her hematocrit was 15% and on physical examination she had a large right flank mass. Abdominal ultrasonography showed a 14 cm by 21 cm solid renal mass with cystic areas, which was confirmed by intravenous pyelography. During cystoscopic examination, bleeding was observed from the right ureteral orifice. A right renal arteriogram showed a renal neoplasm consistent with angiomyolipoma. A right renal tumor surrounded by a large hematoma was subsequently removed and histologic examination resulted in a diagnosis of angiomyolipoma.

Case 3

The patient, a 23-year-old gravida 3, para 2 woman with no evidence of tuberous sclerosis, had the development of irritative bladder symptoms and gross painless hematuria during the 30th week of her pregnancy. Her obstetrician made the diagnosis of cystitis and instituted antibiotic therapy. Severe right flank pain and hypotension developed 48 hours later and her hematocrit fell from 41% to 21%. An abdominal ultrasonogram showed a right retroperitoneal mass and on surgical exploration there was a large renal tumor that had ruptured, producing extensive retroperitoneal hemorrhage. An oophorectomy was done and the kidney was removed. The tissue diagnosis was angiomyolipoma. The pregnancy was otherwise uneventful and the patient was delivered of a healthy female infant at term.

Discussion

Angiomyolipoma occurs in about 80% of patients with tuberous sclerosis. In these patients the tumors tend to be multiple, bilateral, less than 2 cm in diameter and asymptomatic. However, 50% of the tumors occur in patients who do not have tuberous sclerosis and in this setting they are most often single, unilateral and may reach 20 cm in diameter. These tumors come to clinical attention because of their size or associated symptoms.[6] Histologically, they are classified as hamartomas—tumorlike malformations composed of an abnormal mixture of the normal constituents of the kidney. The tumors are usually smooth, oval and encapsulated and are located in the renal parenchyma. They enlarge by expansion rather than by invasion and rarely, if ever, metastasize. The tumor is occasionally found in regional lymph nodes and has been reported in the spleen. Whether this represents a multicentric origin or true metastasis remains unclear.[7,8] The tumors consist of smooth muscle, fat and blood vessels in variable proportions within a supporting stroma of connective tissue. Of particular interest is the vascular component that consists of tortuous arterioles with walls of varying thickness. Few, if any, mitotic figures are seen.

Angiomyolipomata characteristically appear as ill-defined radiolucent areas of fat density on plain films of the abdomen.[9] Renal tomography has been used to accentuate this characteristic.[10] The appearance of multiple arterial aneurysms, the whorled "onion peel" effect of the venous phase and an atypical response to ephedrine sulfate on renal angiography have also been used to establish the diagnosis.[11] Ultrasonography has also been helpful in diagnosing these tumors because the high fat content gives rise to localized internal echos. Computed tomography may be particularly applicable

(Lewis EL, Palmer JM: Renal angiomyolipoma and massive retroperitoneal hemorrhage during pregnancy. West J Med 1985 Nov; 143:675-676)

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during pregnancy because it reduces the radiation exposure of patients.[12]

One of the reported complications of renal angiomyolipoma is hemorrhage. It has been speculated that the increased blood volume during pregnancy may be a factor in causing these tumors to rupture and bleed. The pronounced increase in renal blood flow also seen in pregnancy may further increase the threat of hemorrhage. Hemorrhage occurs almost exclusively in patients who have large, single, unilateral lesions and who do not have tuberous sclerosis. Three cases have been reported in which bleeding was so massive that an emergency nephrectomy was required. The symptoms associated with hemorrhage are remarkably uniform, with the abrupt onset of flank pain, abdominal or flank mass and hypotension. Recovery is the rule if an early diagnosis is made.

Fortunately, massive retroperitoneal hemorrhage during pregnancy is uncommon. In addition to angiomyolipoma, reported causes include spontaneous rupture of hydronephrotic kidneys, rupture of renal aneurysms, ruptures of renal vessels and other less common vascular accidents.[13] There appears to be no relationship between rupture of an angiomyolipoma and the patients' age, parity or stage of gestation. Because rupture rarely occurs in the tumor variant most often associated with tuberous sclerosis, there may be little advantage in a heightened awareness of this complication in a pregnant patient with that disease.

The cases reported here illustrate that rupture of an angiomyolipoma may be one of the more common causes of life-threatening retroperitoneal bleeding during pregnancy. The diagnosis can be supported and often confirmed by appropriate radiographic techniques, and the lives of the mother and child can be saved if there is early surgical intervention.

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Bacillus cereus Pleuropulmonary Infection in a Normal Host

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BACTERIA OF THE GENUS *Bacillus*, with the exception of *Bacillus anthracis*, rarely cause pleuropulmonary infection. Most such cases have occurred in immunocompromised patients. We report here a case of necrotizing pneumonia and empyema caused by *Bacillus cereus* in a patient who had no obvious immunologic compromise.

Report of a Case

The patient, a 67-year-old retired engineer, was admitted to hospital complaining of substernal and right-sided pleuritic chest pain lasting several hours. He had a medical history of coronary artery disease manifested by four myocardial infarctions and severe congestive cardiomyopathy with a left ventricular ejection fraction of 23% previously measured by radionuclide ventriculography. No evidence of acute myocardial infarction was found and the patient was transferred to Veterans Administration Medical Center, Fresno, California.

On physical examination he had no fever or significant chest abnormalities. Jugular venous distension, peripheral edema and ascites were present. An S_3 gallop was noted. Chest roentgenogram showed cardiomegaly and a right pleural effusion associated with a patchy right lower lobe infiltrate. Laboratory studies elicited the following values: leukocyte count, 13,100 per μl (83% segmented neutrophils, 9% bands, 5% lymphocytes and 3% monocytes), and hemoglobin, 15.1 grams per dl. Serum creatinine, 1.2 mg per dl; blood urea nitrogen, 56 mg per dl; albumin, 3.2 grams per dl; total protein, 6.2 grams per dl, and lactate dehydrogenase, 195 units per liter. A diagnostic thoracentesis yielded cloudy amber fluid that had a leukocyte count of 10,143 per μl (91% neutrophils, 9% lymphocytes); protein, 2.9 grams per dl; lactate dehydrogenase, 87 units per liter (serum normal, 83 to 173 units per liter); glucose, 18 mg per dl, and pH, 6.48. A Gram's stain of a pleural fluid specimen showed Gram-positive rods. A tube thoracostomy established adequate drainage of the pleural space. A regimen of gentamicin sulfate (90 mg every eight hours) and cefazolin sodium (1 gram every six hours) was begun.

Pleural fluid cultures produced a pure growth of *B cereus* resistant to penicillins (including those unaffected by penicillinase) and cephalosporins and sensitive to aminoglycosides, chloramphenicol, clindamycin, erythromycin and sulfonamides. After determining the sensitivities of the organism and in view of deteriorating renal function, the gentamicin and cefazolin therapy was discontinued and a regimen of

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erythromycin, 500 mg given intravenously every six hours, was begun. Over the next two weeks the patient's condition gradually deteriorated, as manifested primarily by progressive prerenal azotemia that we felt was due to poor left ventricular function. Treatment with hydralazine hydrochloride and digoxin was ineffective. More aggressive management was not instituted at the request of the patient. Deterioration was relentlessly progressive and the patient died on the 23rd hospital day. An autopsy showed a necrotizing right lower lobe pneumonia with fibrinopurulent material adherent to the right pleural surface, as well as a recent myocardial infarction.

Discussion

Bacteria of the genus *Bacillus,* with the exception of *B anthracis,* rarely cause serious human infections. When they occur, such infections usually fall into one of two categories: local infections (wound infections, meningitis) with a recognized source of inoculation or disseminated infections in immunocompromised patients.[1]

Pleuropulmonary infection caused by *Bacillus* species is unusual. Only ten such cases have been reported. In seven of these cases the causative organism was *B cereus,*[2-8] in two it was *Bacillus subtilis*[3,9] and in one it was *Bacillus sphaericus.*[10] In one of the cases, both *B cereus* and *Clostridium bifermentans* were recovered, making the pathogenic role of *B cereus* unclear.[8]

Of the nine previously reported cases of pleuropulmonary infections caused solely by *Bacillus* species, six were in patients with hematologic malignancy,[2-5,9] one was in a patient taking corticosteroids[10] and one was in a patient with chronic active hepatitis and hepatic cirrhosis.[6] There is but a single prior report of pleuropulmonary infection attributable only to *Bacillus* species in a normal host.[7]

Our patient was chronically ill with ischemic cardiomyopathy. In this respect he resembled the previously reported patient who had pneumonia and empyema from which *B cereus* and *C bifermentans* were recovered.[8] It is possible that congestive heart failure may predispose to opportunistic infection, but such an inference is speculative. Specific analyses of our patient's immune response were not done, but he appeared to be immunologically competent at the time of admission. Progressive azotemia may have increased susceptibility to the infection, defects of cellular and humoral immunity having been documented in patients with renal insufficiency.[11,12]

The antimicrobial susceptibility of *B cereus* recovered from our patient was similar to that previously reported.[5,8,13] Resistance was found to penicillins and cephalosporins. Sensitivity to aminoglycosides, chloramphenicol, clindamycin, erythromycin and sulfonamides was found. Previous cases of pleuropulmonary infection with *B cereus* have been successfully treated with vancomycin,[8] clindamycin[5] and gentamicin.[4]

In spite of appropriate antimicrobial therapy and adequate drainage of empyemic fluid, our patient died. A fatal outcome also occurred in six of the ten previously reported cases of pleuropulmonary infection caused by *Bacillus* species.[2,3,6,7,10] The contribution of the infection to our patient's death is not clear due to severe coexistent heart disease.

Our case indicates that patients without obvious immune incompetence may be susceptible to life-threatening pleuropulmonary infections with bacteria of the genus *Bacillus.* Knowing that *Bacillus* species can cause life-threatening infections in such apparently normal hosts should prevent clinicians from regarding these organisms as mere contaminants when they are recovered from seriously ill patients with pleuropulmonary infections. Recognition of the pathogenic potential of this group of organisms should lead to early institution of antimicrobial therapy and early surgical drainage when appropriate. Such treatment may improve the outcome of this highly fatal infection.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Caring in Medical Practice

TO THE EDITOR: I read with interest the editorial "The Importance of Caring"[1] in the August issue.

The medical profession has been very successful in the last several decades in two ways that may interfere with demonstrating humanistic and caring behavior. Clearly, medical knowledge and technology have expanded the opportunities physicians can offer their patients, lengthened life, provided a higher quality of life in many instances and even eradicated certain diseases. Second, the public has been far better educated about medical problems and, with more discernment, seeks a proper role in medical decisions.

These successes make it more difficult for physicians to fulfill every responsibility within the constraints of traditional appointments, which have not been changed to adapt to such developments. For example, internists still schedule appointments from 45 to 60 minutes for new patients and 10 to 15 minutes for return visits. If cognitive and communicative services were reasonably reimbursed, I wonder what the outcome would be if the time for each appointment were doubled. Caring time might displace some of the fascination with technology and scientific management. Perhaps competition and the possible surfeit of physicians will permit this, as suggested in the editorial. Even corporate providers would need to use such communicative strategies to compete. Patients will declare what pleases them most and ultimately will accept the cost.

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Is Spinal Manipulation Effective?

TO THE EDITOR: Dr J.B. Reuler, in his interesting paper "Low Back Pain," published in the August issue,[1] stated that as a treatment procedure, "Spinal manipulation, of which several methods are used, has also not been proved to be effective."

The effectiveness of spinal manipulation has always been difficult to "prove." Double-blind studies are not truly possible. In fact, many comparative critical studies of various therapies have major weaknesses.[2]

Historically, however, patients have often bypassed the medical profession to attend various healers using manipulative techniques. Bone setters, among other activities, manipulated spines, and James Paget commented in 1867, "Few of you are likely to practice without having a bone-setter for an enemy; and if he can cure a case which you have failed to cure, his fortune may be made and yours marred."[3]

Osteopaths and later chiropractors replaced bone-setters. Spinal manipulation has actually evolved quite independently in various cultures. Recently a black African raised in an isolated Central African region beamed at me after I had used a manipulative technique to help his lower back problem. "I never expected to find *our kind* of treatment over here," he remarked.

He then recalled experiencing similar treatment from a tribal healer, a procedure, he understood, that had been passed down through generations in his tribe.

James Cyriax, in the many printings of his textbook on orthopedic medicine, included a photograph of a 2,000-year-old statue outside a Buddhist temple in Thailand which depicted manipulation of the lumbar spine. There are other examples from separate cultures and eras.

It is difficult to conceive that such a universal remedy could be ineffective.

In the August issue[4] I reported the case of a young man whose back pain was immediately relieved after he had twisted his back and fallen while trying to chase a jackrabbit. He had essentially "manipulated" himself. It is doubtful if the personality of the jackrabbit had any bearing on the result. I am sure many physicians can recall a case where a fall or unguarded twist has brought pronounced relief to a back pain sufferer.

It is a pity that skepticism about manipulation has deterred many a physician from learning the indications, contraindications and techniques of spinal manipulation. Some of their patients have inevitably attended chiropractors, sometimes with apparent benefit, occasionally with unfortunate results.[5]

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Insulin and the Suicidal Patient

To the Editor: Insulin overdose as a method of attempted suicide, although not common, should be considered as a possibility when treating depressed diabetic patients.[1] We report two cases that illustrate some problems that can arise when a suicidal patient has access to insulin.

Case 1

A 21-year-old woman without a previous history of either psychiatric or medical illness was admitted to hospital unresponsive with a serum glucose level of 22 mg per dl and a generalized seizure. Findings on physical examination were unremarkable except for initial horizontal nystagmus. She was treated with intravenous saline and glucose infusions and improved. Serum glucose determinations over the first 24 hours were of variable range (28 to 197 mg per dl) requiring vigorous medical treatment at times. Serum toxicology screen showed the presence of acetaminophen, ephedrine/pseudoephedrine hydrochloride, phenobarbital and phenytoin presumptively. Blood alcohol level was 221 mg per dl.

In psychiatric consultation carried out after medical stabilization, it was found that the patient had been dismissed from her job two months earlier for heavy alcohol intake. She was unable to find another job and for this reason felt life was worthless. She admitted to auditory hallucinations for the past five years and was hearing commands to kill herself. She took eight prefilled insulin syringes containing 12 units of regular and 30 units of NPH insulin from a diabetic friend and injected them into her temple believing that the insulin would reach her brain quickly and kill her. Additionally, she ingested other medication found in the medicine cabinet. She continued to express suicidal ideation and was transferred to a psychiatric hospital for further treatment.

Case 2

A 41-year-old woman had a history of insulin-dependent diabetes mellitus, alcohol abuse and recurrent depression with multiple suicide attempts. These included overdose with pills and drinking household cleaner, and a recent attempt in which she locked herself in the trunk of her car, slashed her wrists and throat, and hit herself in the head with a tire iron. She had been treated in the past with antidepressants and electroconvulsive therapy. There was a family history of depression and her mother and sister both committed suicide by pill overdose with alcohol ingestion.

The patient was admitted to the medical service of the hospital for treatment of hypoglycemia with serum glucose determinations of 28 mg per dl and a generalized seizure. On physical examination there were no acute findings. The patient was treated with intravenously given saline and glucose infusions and improved. Serum glucose determinations over the first 48 hours in hospital were of variable range (20 to 258 mg per dl) requiring additional glucose infusions at times. Other test results were unremarkable and the patient was transferred to the psychiatric service because she had expressed suicidal ideas.

She admitted to injecting herself intravenously with "a couple of bottles" of NPH insulin in a suicide attempt. She had a poor appetite and did not adhere to diabetic dietary restrictions in the hospital although she was maintained on insulin. The patient had been admitted to hospital in the psychiatric facility one month earlier for depression and at that time ate poorly while continuing to receive insulin. This led to multiple readjustments of the insulin dosage both during this hospital stay and previously, and numerous fasting serum glucose determinations were found to be below normal.

The patient was treated with electroconvulsive therapy and improved. She later became delusional, however, and again expressed suicidal ideations necessitating long-term treatment.

The preceding cases illustrate the difficulties that can arise when a suicidal patient has access to insulin. The education of the public to increase awareness of this problem might be indicated to prevent further episodes of a similar nature.

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Conversation, the Ailing Humanity

To the Editor: While in the ward the other day, I observed a house officer at the bed of a new patient. The young physician sat far from the elderly gentleman and posed his questions with a loud voice and a peremptory tone. I knew he was trying to be efficient, to get to the point, but I also knew that he would never succeed in making the patient his willing interlocutor. Wondering how many "poor historians" are iatrogenically induced, I walked into a hospital meeting. As usual, coffee, statistics and strategies were served in abundance but there was no time—nor attempt—to foster an ounce of new benevolence among the participants. By then other experiences were coming to mind: attending parties with too many people sitting along the walls of the room, their plates overflowing with food, their curiosity and imagination untried; meeting medical school applicants who have astounding academic records but are not aware of where an older brother or sister is living.

One may question whether we are still willing and able to communicate with each other. Or are we so trapped in busy schedules and programmed behaviors that we forgo the exhilarating chance of knowing each other—and life through the soul of the other? The risk is real, and perhaps here more than in Europe, where the number of opportunities to share at least fragments of one's soul tends to be greater. I remember the outdoor markets, the squares, the cafés: drawing variegate crowds, providing time and place for observing and exploring, gathering and philosophizing. These daily physical opportunities have been kept and nurtured through the centuries, expressions of the spirit of the agora, of its commitment to foster a wealthy dialectic of interpersonal relationships which ensures that no person should remain stranger to the other.

Do these activities appear superfluous in our efficient,

productive environment? If I interpret correctly the success of bumper stickers, reiterating every day their silent messages of likes and loves through the long hours of commute, I shall argue that people do miss the opportunity to talk about themselves. But there is no time, not for talking, not for listening. One then wonders how fulfullingly is our time otherwise spent, for what ultimate goal are we striving and competing. Is the goal to enhance the quality of life? How can we achieve it if we ignore each other's unique needs and hopes? These questions are relevant to our global social demeanor, as they are to our practice of medicine. Diagnosing and treating are restrictive technical synonyms for understanding and healing, whose chances to occur depend upon the full availability of the parties involved. One cannot heal unless one understands, and one cannot understand unless one explores. Nor can one be healed without being understood and, in order to be understood, one must find or be given the opportunity to recount one's self. Reciprocal comprehension and trust are engendered through friendly, unhurried conversations much more than through form-guided anamneses that have little subtlety for matters of the soul.

The problem may be that we are not taught much of the art of conversing. Watching television, playing computer games, technical reading and multiple-choice exams add very little to our dialectic capabilities. But if conversation glows in the artist, it thrives in the amateur. And amateur we can easily become by starting to cultivate the pleasure of discovering our neighbor, our relative, our patient. The first attempts at an unpracticed activity may be clumsy, even embarrassing, but after a while craftmanship develops: the attitude, the tone of voice, the words almost elect themselves from among the many possible, and self-perpetuating ties are established. We should not miss such simple opportunities to add genuineness to the practice of medicine and benevolence to life around us.

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Immune Complex Disease—Adult Still's Disease? Hepatitis B?

TO THE EDITOR: We have recently seen a patient with clinical and laboratory features consistent with adult Still's disease. Results of serologic testing during the course of illness, however, have raised a conundrum that we feel merits emphasis. We hope this case report will be a valuable addition to Dr Larson's review in the May issue.[1]

Report of a Case

A 29-year-old previously healthy man presented with a four-day history of fever, pharyngitis, polyarthralgias and myalgias. He appeared acutely ill with a temperature, taken orally, of 39.9°C. A maculopapular rash was seen on the anterior thorax and proximal upper extremities. Bilateral synovitis of knees and elbows and hepatomegaly with scleral icterus were present. Initial laboratory tests showed anemia, leukocytosis, elevated liver function values, proteinuria and cylindruria. Antistreptolysin O, rheumatoid factor, antinuclear antibodies, cryoglobulins, complement profiles and multiple serologic tests were negative. Tests for hepatitis B surface antigen (HB_sAg) and anti-HB_sAg were negative. All cultures showed no growth. Subsequently, pleuropericarditis with bibasilar rales, pedal edema, an S3 and a three-component rub developed. Splenomegaly was noted. Pharyngitis and rash were evanescent. An x-ray study of the chest showed a left lower lobe infiltrate with effusion and cardiomegaly. An echocardiogram confirmed a pericardial effusion. A 24-hour collection of urine showed 3.2 grams of protein. Open lung, kidney and bone marrow biopsies were carried out and findings were all nondiagnostic. The patient improved with corticosteroids. Repeat anti-HB_sAg and anti-HB_cAg studies were positive with negative HB_sAg. Circulating immune complexes were shown using the C1q-binding assay.

We feel this case satisfies the inclusion criteria of Medsger and Christy.[2] Had we not obtained repeat hepatitis B serologies, a diagnosis of adult Still's disease might have been established by exclusion. But is this diagnosis tenable despite positive hepatitis B serologies?

A case similar to ours has been reported,[3] in which adult Still's disease was described two months after HB_sAg-positive hepatitis, with serologies seven years later showing both anti-HB_sAg and anti-HB_cAg. In view of the variable temporal relationship between hepatitis B infection and related vasculitis,[4] we feel these two cases are compatible with immune complex disease due to hepatitis B.

Many etiologic agents, sharing a common mechanism of disease induction (immune complex formation) are bound, when conjoined with certain constitutional factors, to give rise to identical features. Whether one emphasizes descriptive aspects or putative mechanism of disease is, at our present level of understanding, a matter of personal choice. A diagnostic effort should not stop at the phenomenological level, though we agree with Dr Larson that adult Still's disease is a distinct clinical syndrome. How would he then classify the above two cases?

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Dr Larson Replies

TO THE EDITOR: Drs Lang and Petrozzi report a very interesting case which illustrates one of many problems with the diagnosis of "adult Still's disease." Based on the clinical course and serologic findings, I would classify this patient as having vasculitis and immune complex disease due to hepatitis B. Although elevation of liver enzymes (aspartate aminotransferase and alanine aminotransferase) and acute and chronic hepatitis are seen in patients with adult Still's disease,[1,2] jaundice is not common[1,3,4] except in patients with fulminant hepatic failure or chronic liver disease.[5,6] Most important, although the case does meet the inclusion criteria

of Medsger and Christy, [7] the diagnosis becomes untenable when a better diagnosis, suggesting a mechanism of disease, is available.

I agree that a diagnostic effort should not stop at the phenomenological level.[8] In particular, it is always difficult to make a diagnosis of adult Still's disease with confidence based on a single episode of fever. As I have written elsewhere, correct diagnosis includes recognition of the syndrome as well as exclusion of other possible diseases.[4] Thus, I believe patients with rubella infection[9,10] and hepatitis B infection and their sequelae, even though they meet the syndromic criteria for adult Still's disease, are best considered as having a disease caused by rubella virus or hepatitis B virus, respectively.

Of interest, the American Rheumatism Association recognizes this problem by including "exclusion of other rheumatic diseases" as a criterion for the diagnosis of juvenile rheumatoid arthritis.[11] I believe the same can apply to adult Still's disease with the addition of exclusion of infectious causes, as illustrated by the case reported above. In my own practice, I try to keep an open mind and consider the possibility of an infectious disease as the cause of a flare, even in a patient with long-standing recurrent adult Still's disease.

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Acronyms in Medical Journals

To the Editor: I am becoming more and more frustrated by the increasing use of acronyms in our medical journals. I am wondering if there is any valid justification for their being used. In medical writing there are many time honored abbreviations but their use has repeatedly been discouraged because some may be the same or similar to other abbreviations and errors in reading and interpretation could result.

The current mass of medical literature is almost unnecessarily filled with a perfusion of acronyms. In reading some acronyms, one finds one's self backtracking to earlier portions of the article to refresh one's understanding of their meaning, and then re-reading the text to better understand what was meant. Result: slower reading and impaired continuity and retention of information. I contend that with the exception of some long chemical names, one can read all the basic words of an acronym as fast as the acronym; and if backtracking is needed for understanding, much faster.

I wonder why we so generously use acronyms? It can't be to save ink, or paper, or secretarial efforts, or some of the readers' time. By what criteria do we justify the frequent and at times flagrant use of acronyms?

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Editor's Note

We agree. *WJM* policy is to spell out acronyms wherever this seems reasonable.

MSMW

Coronary Heart Disease and Smoking

To the Editor: Hopkins and co-workers, in the August 1984 issue,[1] interpret their findings as suggesting the existence of a "possibly synergistic interaction of cigarette smoking and family history [of coronary heart disease]" on risk of coronary heart disease (CHD) in the relatives of their CHD probands. Furthermore, they emphasize the likely pronounced benefits of smoking cessation for those with such a positive family history. However, an important methodological problem in their study complicates the interpretation of their results and prevents firm conclusions from being drawn.

Despite relatively careful ascertainment of some risk factor and morbidity information, these authors obtained reliable information on lipid profile—perhaps the most significant CHD risk factor—in only 81 of the 2,473 proband and control relatives. Hyperlipidemia in the other relatives was assessed via questionnaire completed by a single collateral source (that is, a relative), a notoriously unreliable method of obtaining information. Indeed, the authors found that, among these 81 relatives given a medical evaluation, only a fourth of those determined to have hyperlipidemia (undefined) were aware of their condition. Therefore, it is unlikely their collaterals were any more aware of it. Attempting to determine the independent effects on CHD risk of family history without partialling out the influence of lipid levels is simply not possible.

This absence of adequate information on lipid profiles of relatives is problematic in interpreting the study's results. There is a substantial body of evidence which strongly suggests that one synergistic interaction effect on CHD risk involves smoking and *elevated lipids*.[2] Consequently, it would appear likely that the interaction effect of smoking and family history in this study could largely be accounted for by familial aggregation of lipid levels.

The identification of a synergistic interaction between smoking and elevated lipids would imply, as has recently been suggested,[2] that those at risk for the health effects of smoking, and therefore more likely to benefit from cessation, are those with elevated lipids, which is determined not only by heredity but by environmental factors, and *not* necessarily those with a family history of CHD (although these groups likely overlap to a great degree).

It is unfortunate that an otherwise remarkably careful study does not provide clear results. However, advocating CHD prevention efforts for those not necessarily at risk while ignoring others who may be at substantial risk is even more unfortunate.

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* * *

The Authors Reply

TO THE EDITOR: Dr Perkins has raised several important points which we are happy to address. He correctly points out the relative insensitivity of family reporting for elevated serum cholesterol. Only about a third of persons with elevated lipid levels by clinic measurements had been previously aware of their high-risk lipid status. A falsely low prevalence of hyperlipidemia may well have accounted for some of the observed exaggerated risk for cigarette smoking among relatives of male early coronary heart disease (CHD) probands in our study. If the excess risk for smoking in these families was associated with hypercholesterolemia, then a plausible explanation would be readily formulated. Indeed, earlier epidemiologic studies in Honolulu and Puerto Rico had found minimal or no excess CHD risk among cigarette smokers with low serum cholesterol levels (under approximately 180 mg per dl).[1] These observations led to the concept of "permissive" serum cholesterol levels. Serum cholesterol apparently had to be elevated above some minimum value for atherosclerosis to become clinically manifest even with other risk factors present. High lipid levels would logically be expected to act synergistically with cigarette smoking to hasten clinical manifestations of CHD. Various mechanisms relating serum lipids and cigarette smoking to atherogenesis have been forwarded.[2] Dr Perkins's observations to which he alludes will be most interesting.

Elevated serum cholesterol levels cannot, however, explain all the excess risk associated with smoking among CHD prone families in our study. More in-depth examination of several families identified in our original study suggests other important mechanisms operating which account, at least in part, for the magnified risk of cigarette smoking which we reported. One family was identified, for example, with five brothers and one sister, all with coronary disease under age 60. Four had onset by age 42. Three of the six had already died of CHD, two as young as 38 years of age. Serum cholesterol and triglyceride measurements, as well as high density lipoprotein, apolipoprotein A_1 and apolipoprotein B determinations, in living coronary cases as well as 73 other relatives were carried out. There was no consistent relationship between lipid levels and coronary disease occurrence in family members. On the other hand, all the affected persons smoked cigarettes. At least two other families have been tentatively identified in which smoking as a solitary risk factor seemed to have played a dominant, causative role in the family's experience with early CHD (unpublished observations). We would hasten to mention that the serum cholesterol levels observed in these families were in the permissive range but not greatly elevated (between 190 and 289 mg per dl).

At least three other mechanisms for elevated CHD risk have been identified among families screened in our clinic. Familial hypercholesterolemia is fairly common. Early onset hypertension either alone or in conjunction with other risk factors seems to be the common denominator of CHD in some families. Finally, we have characterized two pedigrees in whom low HDL-cholesterol levels (26 mg per dl or less) segregated as a dominant gene phenotype.

Clearly, to assign all the smoking-familial CHD interaction reported in our study to hyperlipidemia would be a gross oversimplification. While we certainly agree that to encourage smoking cessation is extremely important for persons with elevated serum lipids, our studies have opened other avenues for targeted intervention. It is hoped that some of these high-risk families will soon be benefited by intervention efforts designed specifically for their unique problems.

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Sclerosant Solution in Low Back Pain

TO THE EDITOR: I wish to comment on the opinion expressed in answer to the Medical Practice Question "Multiple Injections of Sclerosant Solution," in the June 1985 issue.[1]

The Sclerosant Solution

I agree with the opinion that a solution containing 25% phenol is not acceptable. I am not aware that anybody has advocated such a concentration of phenol. The solution originally described by Hackett and Huang contained 2.5% phenol.[2] Neither phenol nor glycerine are required. A sclerosant solution containing only 25% dextrose gives excellent results.[3,4]

The Hypothesis

- It may not be proved scientifically that low back pain is related to a derangement of the ligamentous structures but this hypothesis is generally accepted by the medical profession as expressed in the diagnosis of low back sprain, sacroiliac sprain, lumbosacral sprain and the like.
- A careful clinical examination permits a differential diagnosis of ligamentous low back pain. The diagnosis of one type of ligamentous pain has been described by Hirschberg and co-workers.[5]
- That injection of sclerosant agents causes inflammatory changes and ultimately fibrosis has been amply documented in the literature. The specific fact that ligaments can be strengthened by injecting sclerosant agents has been proved in laboratory animals by Hackett,[6] Liu and associates[7] and G. Borden (unpublished data, 1985).

Effectiveness

Results of treatment of low back pain with sclerosant agents have been published by Hackett,[6] Barbor[3] and Naeim and associates.[4] The latter study is fairly blind and shows an 85% cure rate in cases of long-standing chronic ligamentous low back pain. Sclerosant therapy is the most effective, most economical and least risky treatment of chronic ligamentous low back pain.

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* * *

To the Editor: I note that in the "Medical Practice Question" dealing with "Multiple Injections of Sclerosing Solutions,"[1] three scientific panels rendered an opinion that the practice was "unacceptable" on the basis of their point that "In fact, there have been no double-blind studies that have documented the safety and effectiveness of this technique."

That is—in fact—incorrect. There was an excellent study by Naeim, Froetscher and Hirschberg published in *The Western Journal of Medicine* in 1982.[2] I would think that panels implying they have made a thorough literature search, but missing a recent study in the very journal in which they are publishing the opinion, should be called upon to do a bit more homework and reconsider their opinion as such additional evidence is presented.

The study by Naeim and co-workers was done on patients with chronic back pain and used remarkably strict criteria. The results suggested that the treatment was exceptionally effective even when the small study was corrected for its size. For those of us dealing with chronic pain, the results were particularly impressive. They come from an investigator who has "earned his spurs" in other areas as well. It might be said that the study can be criticized, repeated or extended, but it should not be ignored.

It is worth mentioning that double-blind studies for injection techniques are difficult to unearth and in a recent search of my own I could not find them for such prevalent procedures as facet blocks, epidural blocks and trigger-point blocks. I may have missed studies as easily as the scientific panels; however, it may well be that "sclerotherapy" is actually one of the more well-documented injection procedures.

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Dr Michael W. Abdalla Replies

To the Editor: The medical practice opinion dealing with sclerosant solution in the June issue[1] is a response to a specific question. Based upon literature available and the expertise of their members, the Advisory Panels on Neurology, Neurosurgery and Orthopedics agreed that the use of multiple injections of a sclerosant solution containing phenol, dextrose, glycerin and pyrogen-free water is unacceptable in the management of neck, back and lower extremity pain.

Though the advisory panels are unaware of double-blind studies that document the safety and efficacy of this technique, Dr Sine suggests that such a study was published by Naeim and co-workers.[2] The study, "Treatment of the Chronic Iliolumbar Syndrome by Infiltration of the Iliolumbar Ligament," is of interest. However, it is not, as claimed, double-blind. It evaluated a small number of patients (16) and it limited its investigation to the injection of lidocaine (with and without dextrose) for low back pain.

The study itself acknowledges that the method of injecting lidocaine with hypertonic dextrose is "used by only a small number of physicians," and it concedes that treatment with dextrose has been discouraged by many physicians for two reasons: effectiveness and safety.

In the event of new scientific evidence, the advisory panels will review and possibly revise their opinion on this issue. Until then, they support the opinion published in June.

We appreciate the comments of Drs Hirschberg and Sine and welcome proponents of this technique to conduct further investigations into its safety and potential for alleviating neck, back and lower extremity pain.

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Intractable Cough

To the Editor: I read with interest the excellent staff conference "Evaluating and Treating Intractable Cough" in the August issue.[1]

I would like to comment on a cause of intractable coughing which I have seen many times—acute or chronic sinusitis.[2,3] The latter diagnosis is sometimes missed because x-ray films of the sinuses are not obtained. In many cases the only symptoms of which patients complain are postnasal discharge and cough. Often adequate antimicrobial therapy with appropriate antibiotics for an adequate length of time (two to four weeks) alleviates the symptoms.

Some authors have called this the sinopulmonary or sinobronchial syndrome. In many cases atopy plays a significant role in precipitating chronic sinusitis.

I have also seen other patients who defy any etiologic trigger and who dramatically respond to local anesthetics sprayed on the pharyngeal area.

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Topics in Primary Care Medicine

Prevention of Osteoporosis and Osteoporotic Fractures

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Osteoporosis is a reduction in bone mass that predisposes to fractures, especially in the hip, vertebrae, distal forearm (Colles' fracture), humerus and pelvis. In the fourth or fifth decade of life all people begin to lose bone, but women from young adulthood on have less bone than men and have an accelerated loss of bone for many years following menopause. With advancing age, an increasingly large proportion of the elderly, especially white women, are likely to sustain a fracture as a result of minimal trauma, such as a fall. These osteoporotic fractures, particularly of the hip, cause considerable disability and many premature deaths. Primary care physicians may play an important role in preventing these fractures by advising patients about ways of preventing bone loss and the falls that precipitate the fractures.

Osteoporotic Fractures

Hip fractures account for more death and disability than all other osteoporotic fractures combined. More than 200,000 cases of hip fracture occur in the United States each year; 75% of these occur in women and half after age 80. Those who suffer hip fractures have a 12% to 20% greater risk of dying within one year of the fracture than patients of similar age who have fractures elsewhere. Of those who were living at home at the time of their hip fracture, 15% to 25% will remain in long-term care institutions, and about half of those who return home will have to depend on other people or devices to walk and take care of themselves.

Colles' fractures are the most common type of fracture among adults before age 75, when hip fractures surpass them in frequency. Few people with Colles' fractures have to be admitted to hospital, and the fracture rarely causes death.

Vertebral fractures can be classified as "complete" compressions of the entire vertebral body or a compression of its anterior or middle section. The prevalence of vertebral fractures is unknown, but by age 70, about 5% of white women will have at least one complete compression fracture, and by age 80, most white women will have at least one partial vertebral deformity seen on spine film. Whether complete or partial, these fractures generally occur spontaneously or as the result of very minimal trauma, such as a cough. Although some may result in back pain that lasts from several weeks to months, many vertebral fractures cause no symptoms. Once deformed, vertebrae never regain their normal shape. In some women, these vertebral deformities and fractures may accumulate, causing loss of height, a kyphotic "dowager's hump" and, occasionally, chronic back pain.

Assessing the Risk of Fractures

On average, an adult white woman has about a 15% chance of suffering a hip fracture and an additional 15% chance of a Colles' fracture during her lifetime. In contrast, men and black women have less than a 5% lifetime risk of a hip or Colles' fracture. The risks of fractures for Asians, Latin-Americans and other racial groups are not known. The incidence of hip fractures increases dramatically with age, so that each year after age 80 a white woman has about a 2% chance of fracturing her hip.

Thin women have slightly less bone mass and a greater risk of osteoporotic fractures than obese women. Women who have had bilateral oophorectomies before their natural menopause have a greater risk of fractures, unless they are given estrogen therapy. Persons with alcoholism are also suscep-

(Cummings SR, Nevitt MC, Haber RJ: Prevention of osteoporosis and osteoporotic fractures [Topics in Primary Care Medicine]. West J Med 1985 Nov; 143:684-687)

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This study was supported in part by the Department of Health and Human Services Administration on Aging grant No. 90-AP-0003.

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tible to osteoporosis and fractures, but whether a more moderate use of alcohol predisposes the bones to fracture is not yet known. Cigarette smokers seem to have less bone mass and a greater risk of fractures than nonsmokers. This may be because, on average, smokers are thinner than nonsmokers and female smokers tend to undergo menopause at an earlier age than nonsmokers. Patients treated with corticosteroids, especially in doses exceeding 15 mg of prednisone a day or an equivalent for more than two years, are more likely to fracture their vertebrae and ribs than other bones. A previous gastrectomy seems to be associated with an increased risk of fracture, but some of this risk may arise because most patients with recurrent ulcer disease are smokers.

Researchers have investigated several other possible risk factors for osteoporotic fractures, including a family history of fractures, low-calcium diets, high-protein diets, a sedentary life-style, little exposure to sunlight, diabetes mellitus, rheumatoid arthritis and the long-term use of caffeine, thyroid supplements and antacids. The evidence that these predispose a person to osteoporosis or osteoporotic fractures is not strong. Contrary to earlier concerns, breast feeding and parity do not increase the risk of osteoporotic fractures; in fact, the evidence suggests that they may lower the risk slightly.

Prevention of Osteoporosis and Fractures

Two strategies for preventing osteoporotic fractures are to increase or preserve bone strength, and to prevent the injuries that cause fractures. Measures that may substantially increase bone mass are still experimental. Therefore, current efforts to strengthen bone must be directed at preventing bone loss; these include estrogen therapy, calcium supplementation, exercise and other approaches (Table 1).

Estrogen Therapy

Estrogen appears to stop postmenopausal bone loss for as long as a woman continues to take it. Effective prevention of bone loss necessitates daily doses equivalent to 0.625 mg of conjugated estrogen, or 25 μg of ethinyl estradiol or mestranol. One recent study suggests that doses of conjugated estrogen as low as 0.3 mg a day may prevent bone loss if supplemented with 1,500 mg of elemental calcium a day. When estrogen therapy is used for at least five years after menopause, the risk of hip fracture appears to be reduced by about 50%. If a woman stops taking estrogen, bone loss resumes at about the same rapid rate that follows menopause.

The postmenopausal use of estrogens does not substantially increase the risk of breast cancer. The use of estrogen is associated with about a three to five times increased risk of endometrial carcinoma, a risk that can probably be reduced by periodic administration of progestins.

Many studies have suggested that postmenopausal estrogen therapy reduces the incidence of coronary heart disease and lowers overall mortality rates. If confirmed by additional evidence, this benefit would be more important than all of the other risks and benefits of estrogen therapy combined. There is concern, however, that the addition of progestins may have adverse effects on lipids, which might negate this benefit of estrogen therapy. (See Haber, 1985, for a more detailed discussion of postmenopausal estrogens.)

Calcium Supplementation

In the United States, women consume an average of 475 to 575 mg of calcium per day. However, studies suggest that, on average, white women require about 1 gram of calcium a day before menopause and 1.5 grams a day after menopause to prevent a slow, steady net loss of calcium from their bodies. Women treated with at least 750 mg of supplemental elemental calcium a day have generally been found to lose bone more slowly than untreated women. But calcium supplementation is not as effective as estrogen therapy in preventing bone loss, and there has been little evidence that increases in calcium intake can reduce the risk of osteoporotic fractures.

Generic calcium carbonate is the least expensive form of calcium supplementation (Table 2). Calcium carbonate is 40% elemental calcium; therefore, to obtain 1 gram of elemental calcium, a person must take 2.5 grams of calcium carbonate—two to five tablets a day, depending on the particular preparation. The tablets should be taken with meals, and many experts recommend taking these supplements in divided doses. A similar quantity of calcium can be obtained from three cups of milk or yogurt a day. Although green vegetables contain a high concentration of calcium, the calcium may not be as available for absorption because it is bound to oxalate, which is also found in high concentrations in those vegetables. Persons with renal failure, hyperparathyroidism or a history of calcium-containing kidney stones should not increase their

TABLE 1.—*Summary of Clinical Strategies to Prevent Osteoporotic Fractures*

Premenopausal Women
Avoid smoking and excessive alcohol consumption
Exercise regularly (at least 30 minutes 3 times a week)
Have adequate calcium intake (about 1 gram of total elemental calcium a day)
Perimenopausal and Early Postmenopausal Women
Avoid smoking and excessive alcohol consumption
Exercise regularly (at least 30 minutes 3 times a week)
Have adequate calcium intake (about 1.5 grams of total elemental calcium a day)
White women should consider and discuss estrogen therapy with physician
Elderly Women
Avoid smoking, excessive alcohol consumption and sedative drugs
Exercise regularly
Have adequate calcium intake (about 1.5 grams total elemental calcium a day)
Treat disabilities that may cause falls
Correct possible hazards that may cause falls in the home.

TABLE 2.—*Calcium in Foods and Supplements*

Item	*Approximate Serving per Gram of Elemental Calcium*	*Approximate Cost per Gram of Elemental Calcium*
Milk	3 cups	$ .30- .40
Cheese	5 oz	.80-1.20
Yogurt	3 cups	1.20-1.80
Green vegetables	2 cups (cooked)	.50-1.00
Generic calcium carbonate	2.5 grams (4 to 7 tablets)	.05- .25
Tums Antacid Tablets *	5 tablets	.15
Other brand names	2.5 grams (2 to 5 tablets)	.25-1.00

*Norcliff Thayer brand of calcium carbonate, 500 mg ("regular"), or 750 mg ("extra strength").

calcium intake except in unusual circumstances, and then only under the careful supervision of a physician who is experienced in the management of these disorders. In others, an increase in dietary calcium of as much as 3 grams a day is generally safe and free of side effects. Measuring serum or urine calcium concentrations is rarely necessary in those who decide to take calcium supplements or increase their dietary intake of calcium.

Exercise

Astronauts and people confined to bed lose about 1% of their bone mass each week. Athletes, however, appear to have somewhat greater bone mass than nonathletes, although it tends to be localized to the part of the skeleton that bears the greatest load. For example, tennis players have slightly greater than normal bone mass in their playing arm, but normal bone mass in their other arm.

Results of a few small-scale trials have suggested that postmenopausal women may reduce their bone loss by doing any of several types of exercise for 30 to 60 minutes three times a week. Whether regular exercise might reduce the risk of fractures is not yet known. Still another potential benefit of regular exercise is that it might decrease the number of falls by preserving or improving neuromuscular conditioning.

Other Therapies

People who have used thiazide diuretics long term apparently have somewhat greater bone mass than those who have not, but the efficacy of thiazides in preventing osteoporosis and osteoporotic fractures requires further study before they can be recommended for this purpose.

In pharmacologic doses, sodium fluoride induces the formation of new but histologically abnormal trabecular bone and reduces the incidence of new vertebral deformities in postmenopausal women who have had vertebral fractures. However, these doses of fluoride may cause gastritis, gastrointestinal bleeding or periarthritis, and there is concern that fluoride may paradoxically weaken the outer cortical layers of bone and increase the risk of hip fracture. Therefore, fluoride therapy should be given only by specialists experienced in its use.

Vitamin D supplements do not prevent bone loss or fractures in postmenopausal women, but an intake of 400 to 1,000 units a day, as contained in multivitamin preparations, may be useful in preventing osteomalacia in elderly patients who have no exposure to sunlight and whose diets are deficient in vitamin D. Calcitriol (1,25-dihydroxyvitamin D) is the most potent metabolite of vitamin D. Serum concentrations of calcitriol decline with aging, and some recent studies suggest that the use of calcitriol may increase bone mass in women with vertebral fractures. Because of its tendency to cause hypercalcemia and its expense, calcitriol is still considered an experimental therapy.

Prevention of Falls

For the very elderly (80 years and older), most of whom already have osteoporosis, measures to prevent falls may be more beneficial than therapies to prevent further bone loss. Some patients may have correctable impairments of visual acuity. A very few patients will have disorders such as Parkinson's disease or recurrent arrhythmias that can be specifically treated to prevent falls. The use of alcohol or sedative hypnotics and major tranquilizers, which predispose especially to falls at night, should be avoided or minimized. Because most falls occur at home, attempts to reduce environmental hazards should focus on the elderly person's home. Obvious hazards such as loose rugs, wires or any obstacle on the floor should be removed, nonslip surfaces and railings on stairs and in bathrooms installed, and all rooms, hallways and stairways adequately lit. (See Rubenstein, 1983, for a more detailed discussion of the prevention of falls.)

Screening for Osteoporosis

Various noninvasive radiologic and nuclear imaging techniques are available for measuring bone mass, and measuring bone mass in postmenopausal women is now routinely done in a growing number of medical centers. However, the value of these techniques is uncertain. It has not been established that these measurements can identify those who have the greatest risk of hip or forearm fractures. In fact, these noninvasive techniques have shown that loss of bone mass is about the same in elderly women who have fractured hips and women of similar age who have no fractures. Direct measurement of spinal bone mass by computerized scanning or dual-photon absorptiometry might be a more useful technique of identifying women with the greatest risk of vertebral deformity, but they are relatively expensive. Until studies have shown that measuring bone mass can indicate the risk of future hip and other osteoporotic fractures, their value in making decisions about the prevention of osteoporosis in particular cases is uncertain, and they should not be ordered routinely for postmenopausal women.

Clinical Strategies to Prevent Osteoporotic Fractures

Because the postmenopausal use of estrogen appears to be the most effective method of preventing bone loss and hip fractures, physicians should discuss the possible benefits and risks of long-term postmenopausal estrogen therapy with all white women at the time of menopause. Thin white women, women who have had bilateral oophorectomies before their natural menopause and women who have disorders that may predispose them to falls should consider estrogen therapy in a dose of 0.625 mg of conjugated estrogens or equivalent per day. Bone loss slows and may stop after age 70 and there is no strong evidence that estrogen therapy is beneficial when started after that age. Women with their uterus intact should be advised of the risks of endometrial cancer associated with the use of estrogen alone, and of the unknown cardiovascular risks of the cyclic addition of a progestin. If progestins are used, they should be taken in doses not greater than the equivalent of medroxyprogesterone acetate, 10 mg a day for at least 10 days, every one to three months.

Because the decision to use hormones requires long-term compliance and balancing of risks and benefits, and because hormones may produce side effects such as resumed or continued menstruation, each woman should actively participate in the decision by carefully considering these advantages and disadvantages and discussing her preferences with her physician.

Increasing calcium intake with low-fat dairy products or calcium supplements is generally safe and inexpensive, al-

though of less certain value than estrogen, and it can be recommended to almost all white women of any age. It is not necessary to monitor serum or urine calcium concentrations during calcium therapy unless the patient has renal disease or other conditions known to predispose to hypercalcemia or kidney stones. Regular exercise should be recommended to all patients largely because of its many other potential health benefits.

The increased risk of osteoporotic fractures associated with cigarette smoking and alcoholism provides one more reason why physicians should actively counsel patients to quit smoking and avoid heavy consumption of alcohol.

In the very elderly, prevention of fractures should focus on treating specific disorders that predispose patients to fall, avoiding sedative medications and ensuring that homes are well lit and free from the common hazards that cause falls.

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Medicine in Perspective

'I and My Sciatica'

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Herman Melville (1819 to 1891) after early success was nearly forgotten and little appreciated in his lifetime, yet his works have received new interest in the past half century. He wrote eight novels—the most famous, his masterpiece *Moby Dick* (1851)—several volumes of poetry and a collection of short stories. The novella *Billy Budd* was published 30 years after his death.

The Melville family lived in Albany, New York. After his father died when Melville was 12 years old, the family was in severe financial need; Melville worked at several jobs without much success. At age 19, he signed on as a common sailor aboard a cargo ship bound for Liverpool and back; he later made several whaling voyages. The experiences of his sailing days were used in his novels when he began his writing career in 1844 at age 25.

Melville was a vigorous and robust young man in whom back pain later developed. He mentions back pain, rheumatics and sciatica in his early works and may have had some trouble with his back before the first of many disabling bouts of back pain.

After quitting the sea and marrying in 1847, he moved to New York City where he set up housekeeping with his wife, his brother who was also newly married, his mother and his four sisters. He established a strict schedule of writing that kept him at his desk from 8:30 in the morning to 4:00 in the afternoon. He wrote his first six books between 1844 and 1851. Only the first two books, *Typee* and *Omoo,* were popular successes. Even *Moby Dick,* the sixth book, was not well received.

In *Mardi* (1849), his third book, Melville describes courtiers required to kneel before the throne who complain "our knee pans are stiff with sciatics" and their joints make "that strange crackling and firing off of bone balls and sockets, ever incident to the genuflections of rheumatic courtiers." A stone image of a god "looked as if sore harassed with sciatics and lumbagoes." At a burial place, the travelers were told, "old men zealously donning their raiment immediately after immersion [in consecrated waters] became afflicted with rheumatics; and instances were related of their falling down dead, in this their pursuit of longevity." He described a writer whose "rigidity of style" was due to writing while sitting on a straight-backed bench "when ill of a lumbago, and a crick in the neck."

In *White Jacket* (1850), the narrator was refused permission to waterproof his jacket by a navy lieutenant and blames him for all his soakings and drenchings: ". . . every twinge of rheumatism, which I still occasionally feel, is directly referable to him."

In *Moby Dick* (1851), the carpenter criticizes the artificial legs made ashore: "Those buckskin legs . . . soak water, they do; and of course get rheumatic, and have to be doctored with washes and lotions, just like live legs."

In *Pierre* (1852), the narrator has "some inklings of what it might be, to be old, and poor, and worn, and rheumatic, with shivering death drawing nigh, and present life but a dull and a chill!" He says writers become reckless about their health, remain at their desks—"victims to headache, and pain in the back."

In *Bartley, the Scrivener* (1853), one of the law copyists constantly adjusts his desk to alleviate the ache in his back. "If for the sake of easing his back, he brought the table-lid at a sharp angle well up toward his chin, and wrote there like a man using the steep roof of a Dutch house for his desk, then he declared that it stopped the circulation in his arms. If now he lowered the table to his waistbands, and stooped over it in writing, then there was a sore aching in his back."

In the short story "Cock-A-Doodle-Do" (1853): "Ah! there's that twinge of the rheumatics in my right shoulder. I got it one night on the North River, when, in a crowded boat, I gave up my berth to a sick lady, and stayed on deck till morning in drizzling weather. There's the thanks one gets for charity! Twinge! Shoot away, ye rheumatics! Ye couldn't lay on worse if I were some villain who had murdered the lady instead of befriending her."

In *The Confidence Man* (1857), the narrator discusses Polonius (of Shakespeare's *Hamlet*) who had a stroke and became a "fly-blown old fop": "His vile wisdom is made the viler by his viler rheumatism." He describes a kind of "invalid Titan in homespun": "Why, there is no telling, but the stranger was bowed over, and might have seemed bowing for the purpose of picking up something, were it not that, as arrested in the imperfect posture, he for the moment so remained; slanting his tall stature like a mainmast yielding to the gale, or Adam to the thunder"—a posture suggesting ankylosing spondylitis.

The Melvilles moved to a farm near Pittsfield, Massachusetts, in 1850. In February 1855, according to his wife's memoir, "he had his first attack of severe rheumatism in his back—so that he was helpless." In June 1855, he experienced a severe attack of sciatica and was again incapacitated. The

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family was also concerned about his mental state, especially after *Pierre*, which had offended nearly everyone who read it and proved a critical and financial disaster. The family called their neighbor, Oliver Wendell Homes, who was Professor of Anatomy and Dean of Harvard Medical School, to examine Melville especially about his sanity. Melville had criticized and satirized medicine and doctors in his books; he appeared to have no better regard for Holmes. During the months he was limited by back pain and sciatica, Melville wrote the most genial and intimately personal of his magazine pieces, published in *Putnam's Magazine* in March 1856 and entitled "I and My Chimney," which made literary capital of his predicament.[1] Melville's writings are often allusive and allegorical with many classical and philosophical references. The busybody wife of the story represents his mother who lived with him and constantly made suggestions on rearranging the house. Mr Hiram Scribe is Doctor Holmes.

The story begins, "I and my chimney, two gray-headed old smokers, reside in the country. We are, I may say, old settlers here; particularly my old chimney, which settles more and more every day." The chimney is 12 ft square at the base and 4 ft square at its top, with dual fireplaces connecting the double houses on either side of it. The chimney dominates everything in view, except the "Greak Oak" and "Ogg Mountain," including the narrator; the chimney is the true host of the house. The huge bricks (or vertebrae) of the chimney are no longer used in the building of fireplaces. Because the old roof leaked around it, the chimney had been razeed by a former owner, removing some 15 ft of its top—"a regicidal act of beheading his royal old chimney." The "surgical operation" brought into open air bricks not made of weather-brick, and soon the chimney showed "blotchy symptoms akin to the measles" and began to decay "like a wax nose," requiring another surgical operation: "Unfortunately for the expression—being put on by a squint-eyed mason who, at the same time, had a bad stitch in the side—the new nose stands a little awry, in the same direction."

He occasionally goes down into his cellar to survey the vast square of masonry and wonders at it. "It has a druidical look, away down in the umbrageous cellar there, whose numerous vaulted passages and far glens of gloom, resemble the dark, damp depths of primeval woods." His neighbor chides him for digging around the base of the chimney:

> "Ah, loosening the soil, to make it grow. Your chimney, sir, you regard as too small, I suppose; needing further development, especially at the top?"
>
> "Sir!" said I, throwing down the spade, "do not be personal. I and my chimney . . ."
>
> "Personal?"
>
> "Sir, I look upon this chimney less as a pile of masonry than as a personage. It is the king of the house. I am but a suffered and inferior subject."

He keeps his wines in a small closet in the chimney: "Better for wines is it than voyages to the Indias; my chimney itself a tropic. A chair by my chimney in a November day is as good for an invalid as a long season in Cuba. . . . Ah, a warm heart has my chimney."

His wife dislikes the chimney because it blocks her parlor and she envisions a great hall connecting the two houses. Though nearly as old as himself, she has the spirit of his "young sorrel mare. . . . Though she comes from a rheumatic family, she is as straight as a pine, never has any aches; while for me with the sciatica, I am sometimes as crippled up as any old apple tree." He reflects that his wife would have made the perfect match for Peter the Great or Peter Piper: "How she would have set in order that huge littered empire of the one, and with indefatigable pains-taking picked the peck of pickled peppers for the other." He is satisfied with the way things are, and his wife must have all things new: "Old myself, I take to oldness in things; for that cause mainly loving old Montaigne, and old cheese, and old wine; . . . and very fond of my old claw-footed old chair, and old club-footed Deacon White, my neighbor." Yet his wife has a spite against all these things and, especially, "above all, high above all, would fain persecute, unto death, my high-manteled old chimney."

At last, his wife proposes to abolish the chimney. " 'What!' said I, 'abolish the chimney? To take out the backbone of anything, wife, is a hazardous affair. Spines out of backs, and chimneys, out of houses, are not to be taken like frosted lead-pipes from the ground. Besides,' added I, 'the chimney is the one grand permanence of this abode. If undisturbed by innovators, then in future ages, when all the house shall have crumbled from it, this chimney will still survive—a Bunker Hill Monument. No, no, wife, I can't abolish my back-bone.' "

His wife persuades him to allow a master-mason, "a rough sort of architect," to give a preliminary consideration—Mr Hiram Scribe (Doctor Holmes). He takes Scribe on a tour of the chimney, starting in the basement (his low back):

> We seemed in the pyramids; and I, with one hand holding my lamp overhead, and with the other pointing out, in the obscurity, the hoar mass of the chimney, seemed some Arab guide, showing the cob-webbed mausoleum of the great god Apis.
>
> "This is a most remarkable structure, sir," said the master-mason, after long contemplating it in silence, "a most remarkable structure, sir."
>
> "Yes," said I, complacently, "every one says so."
>
> "But large as it appears above the roof, I would not have inferred the magnitude of this foundation, sir," eying it critically.
>
> Then taking out his rule, he measured it . . .
>
> To be brief, after no small ciphering, Mr Scribe informed me that my chimney contained, I am ashamed to say how many thousand and odd valuable bricks . . .
>
> "Well, sir," said he, a sort of feeling his way, and, to help himself, fumbling with his hat, "well, sir, I think it can be done."
>
> "What, pray, Mr Scribe; *what* can be done?"
>
> "Your chimney, sir; it can without rashness be removed, I think."
>
> "I will think of it, too, Mr Scribe," said I, turning the knob, and bowing him towards the open space without, "I will *think* of it, sir; it demands consideration; much obliged to ye; good morning, Mr Scribe."

His wife and daughters are delighted that Scribe can remove the chimney and demand to know when the removal will start, but his opposition to the idea returns. His wife declares that as long as the chimney stands, it is a monument to his broken pledge and either she or the chimney should go:

> Finding matters coming to such a pass, I and my pipe philosophized over them awhile, and finally concluded between us, that little as our hearts went with the plan, yet for peace's sake, I might write out the chimney's death warrant, and, while my hand was in, scratch a note to Mr Scribe. . . .
>
> To my note, Mr Scribe replied in person.
>
> Once more we made a survey, mainly now with a view to a pecuniary estimate.
>
> "I will do it for five hundred dollars," said Mr Scribe at last, again hat in hand.
>
> "Very well, Mr Scribe, I will think of it," replied I, again bowing him to the door.
>
> Not unvexed by this, for the second time, unexpected response, again he withdrew, and from my wife and daughters again burst the old exclamations.
>
> The truth is, resolve how I would, at the last pinch I and my chimney could not be parted.

For a time, his wife did not disturb him, but he suspected she was collaborating in secret with Scribe:

At last, smoking my pipe one morning, I heard a rap at the door, and my wife, with an air unusually quiet for her, brought me a note. As I have no correspondents except Solomon, with who, in his sentiments, at least, I entirely correspond, the note occasioned me some little surprise, which was not diminished upon reading the following:

". . . It is my solemn duty to warn you, sir, that there is architectural cause to conjecture that somewhere concealed in your chimney is a reserved space, hermetically closed, in short, a secret chamber, or rather closet. How long it has been there, it is for me impossible to say. What it contains is hid, with itself, in darkness. But probably a secret closet would not have been contrived except for some extraordinary object, whether for the concealment of treasure, or what other purpose, may be left to those better acquainted with the history of the house to guess . . ."

This undoubtedly refers to the secret chamber of Melville's state of mind or sanity.

His wife and daughters were elated and renewed their persistent demands to remove the chimney:

That my wife wished to get rid of the chimney, it needed no reflection to show; and that Mr Scribe, for all his pretended disinterestedness, was not opposed to pocketing five hundred dollars by the operation, seemed equally evident. That my wife had, in secret, laid heads together with Mr Scribe, I at present refrain from affirming. But when I consider her enmity against my chimney, and the steadiness with which at the last she is wont to carry out her schemes, if by hook or by crook she can, especially after having been once baffled, why, I scarcely knew at what step of hers to be surprised.

Of one thing only was I resolved, that I and my chimney should not budge.

He writes to Scribe:

Chimney Side, April 2.

Mr Scribe.

Sir:—For your conjecture, we return you our joint thanks and compliments, and beg leave to assure you, that

We shall remain
Very faithfully,
The same,
I and my Chimney.

His wife indignantly insists Scribe can find the secret closet, Melville bets he cannot (doubting Scribe's calculations and his "science").

"Agreed, wife," returned I, knocking my pipe-bowl against the jamb, "and now, to-morrow, I will a third time send for Mr Scribe. Wife, the sciatica takes me; be so good as to put this pipe on the mantel."

Scribe returns; the narrator asks him to verify the exact location of the secret closet. Scribe repeats his survey and finds a discrepancy in his calculations. The narrator demands to know the exact location of the closet and points out to Scribe a number of exceptions to Scribe's calculations. Scribe has been embarrassed and his "science" has failed him. He decides to buy up the decision of Scribe (and his ethics):

"Sir," said I, "really I am much obliged to you for this survey. It has quite set my mind at rest. And no doubt you, too, Mr Scribe, must feel much relieved. Sir," I added, "you have made three visits to the chimney. With a business man, time is money. Here are fifty dollars, Mr Scribe. Nay, take it. You have earned it. Your opinion is worth it. And by the way," as he modestly received the money—"have you any objections to give me a—a—little certificate—something, say, like a steam-boat certificate, certifying that you, a competent surveyor, have surveyed my chimney, and found no reason to believe any unsoundness; in short, any—any secret closet in it. Would you be so kind Mr Scribe?"

He framed the certificate and hung it on the chimney to forever put to rest the stratagems of his wife:

But, no. Inveterately bent upon the extirpation of that noble old chimney, still to this day my wife goes about it, with my daughter Anna's geological hammer, tapping the wall all over, and then holding her ear against it, as I have seen the physicians of life insurance companies tap a man's chest, and then incline over for the echo. Sometimes of nights she almost frightens one, going about on this phantom errand, and still following the sepulchral response of the chimney, round and round, as if it were leading her to the threshold of the secret closet. . . .

The truth is, my wife, like all the rest of the world, cares not a fig for my philosophical jabber. In dearth of other philosophical companionship, I and my chimney have to smoke and philosophize together. And sitting up so late as we do at it, a mighty smoke it is that we two smoky old philosophers make. . . . Scarce a day I do not find her with her tape-measure, measuring, for her grand hall, while Anna holds a yard-stick on one side, and Julia looks approvingly on from the other. . . . Anonymous letters arrive, threatening me with I know not what, unless I remove my chimney. Is it my wife, too, or who, that sets up the neighbors to badgering me on the same subject, and hinting to me that my chimney, like a huge elm, absorbs all moisture from my garden? At night, also, my wife will start as from sleep, professing to hear ghostly noises from the secret closet. Assailed on all sides, and in all ways, small peace have I and my chimney.

He finds a drawer full of plans and estimates for the removal of the chimney, and once came home to find his wife in counsel with an "architectural reformer" about his chimney. Another time, he was nearly struck by bricks (literary critics—and many there were) thrown down from the top of the chimney by workmen in the process of its removal:

Aye, indeed, thinking of those three brickbats, I and my chimney have had narrow escapes.

It is now some seven years since I have stirred from home. My city friends all wonder why I don't come to see them, as in former times. They think I am getting sour and unsocial. Some say that I have become a sort of mossy old misanthrope, while all the fact is, I am simply standing guard over my mossy old chimney; for it is resolved between me and my chimney, that I and my chimney will never surrender.

Holmes's was one of several medical opinions sought by the family. Lemuel Shaw, Melville's father-in-law who was the Chief Justice of the Supreme Court of Massachusetts, and Melville's wife were very concerned about Melville's health and sanity. The doctors concluded he was not insane and was in command of his mental faculties, although Melville thought himself "slightly insane." A farmer with a bad back, Melville became irritable and moody; he sold half of the farm in 1856 to lessen his burden. Unable to do much work, he was sent on a trip to Europe "for his health" in October 1856. He frequently complained of pain and soreness of his eyes, these being "tender as pidgeon's eggs."

In April 1858, aged 39, he experienced another severe crick in the back and, according to his wife, never regained his former strength. The disabling back pain returned again in the fall of 1858. Melville was so limited by the back ailment that he gave up the farm in December 1861 and moved to New York City where he lived the rest of his life. Soon after arriving in New York, he was "ill with rheumatism" for over a month.

Melville had an attack of "erysipelas" in the spring of 1878 that prevented him from using his hands for several months. He was limited for a time in 1884 with "a kind of rheumatic gout" and that year was unable to write for several months because of another severe attack of "erysipelas." A respiratory tract infection developed in December 1890, later diagnosed as "heart enlargement," and he died September 28, 1891, of "cardiac dilation, mitral regurgitation."

After the early success of his sea stories and tales of adventures among the cannibals, Melville's later writings were so strange and bizarre that he lost his following. Not until 1920 was his genius recognized when renewed interest developed in the works of one of America's most important authors. He expressed a disdain for the rheumatics, castigated himself for having the disorder and blamed others for his twinges. His back did not trouble him as much in his later years. Melville included much of this experience in his works and the back pain that plagued him for so long played a role in many of his stories, especially "I and My Chimney."

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Information

A Comparison of Men and Women Physicians' Management of Patient Death

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WOMEN AS PHYSICIANS have been characterized as being more humane than their male counterparts. With the great increase in the number of women in medicine during the past decade, the behavioral characteristics of women could have a pronounced effect on medical practice.[1] Rhetoric extolling the sensitivity, nurturing qualities and humane attributes of women physicians is abundant.[2] Although a few studies have reported differences in attitudes of men and women physicians regarding humane issues,[3,4] no prior study has been done of gender-related differences in any aspect of patient care.

We selected the management of patient death to explore gender-associated physician differences. Family needs for sensitivity and effective communication are great after a loved one's death. A physician's response to these needs is one aspect of humanism. If the nurturing stereotype is true, women physicians should have greater personal contact, be more available or have greater follow-up with families following their patients' deaths. We surveyed physician pairs matched for specialty, age and number of deaths to assess any differences between the sexes in attitudes and practices following patient death.

Physicians and Methods

All women physicians (N = 168) listed in 1982 by the Oregon Board of Medical Examiners in the specialties of family practice, general practice, general surgery, general internal medicine and obstetrics and gynecology were identified. The Board lists each recognized medical and surgical subspecialty separately. Physicians practicing a subspecialty are excluded from the general specialty listings and were not included in our study.

We excluded the women authors and three other women colleagues who were aware of our study goals and design (N = 5). Thus, 163 women physicians were mailed the questionnaire, and 133 (82%) responded to the first or second mailing. To obtain a valid sample of practice management, only women who had completed their house-staff training and had at least one patient die in the preceding year were included in the study. As a consequence, 28 respondents who were still in training and 31 who had had no patient deaths in the preceding 12 months were excluded. One other female respondent was excluded due to incomplete responses on the questionnaire. The resultant study population included 73 women practicing in one of the primary care specialties.

The male physicians were taken from a pool obtained by random sample of these same five primary care specialties listed by the Oregon Board of Medical Examiners. This selection process has been previously described.[5] In all, 110 men met requirements for inclusion in the study and served as the matching pool. Female-male physician pairs were matched for specialty, age and number of practice deaths (N = 69 pairs). A suitable male counterpart could not be found for four of the women, and they were excluded.

The survey instrument contained 35 questions addressing three general areas. Initial questions dealt with physician demographics: sex, age, specialty and number of patient deaths in the preceding 12 months. Reported patient deaths were further defined with questions on the frequency of in-hospital deaths and the percentage of anticipated deaths. The remaining questions surveyed physician attitudes and practices following the death of a patient—the means of notifying the family, subsequent family contact, anxiety level of the physician and extent of prior training in death and dying.

Demographic characteristics were individually compared with physician attitudes and reactions following patient death. Men and women were classified by the specialty they indicated on the questionnaire, rather than the specialty reported by the Board, when discrepant. Responses by men and women to scaled variables were compared via the paired *t* test. Categorical responses were compared by using the $\varkappa$ statistic to measure overall level of agreement between men and women.[6] McNemar's test was used to measure directional trends in responses to categorical variables.[7]

Results

The men and women physician pairs were closely matched for demographic characteristics (Table 1). There was no significant difference in their age ($P = .6$), and the physician pairs were well matched for specialty ($\varkappa = .77$) and number of patient deaths in the preceding year ($\varkappa = .92$). Analyzing the circumstances of the patient deaths shows comparability between women and men physicians. Most patient deaths were anticipated by their primary physicians, and the frequencies of expected deaths were similar for men and women physicians ($P = .3$). Only 10% of men and 16% of women reported that most of their deaths were unexpected. Most patients died in hospital. Out-of-hospital deaths, however, were more frequent in the practices of women physicians ($P = .01$), with 7% of men and 27% of women reporting that most of their patients died away from hospital.

Initial communication with the deceased's family was reported to provoke moderate anxiety for most physicians.

(Tolle SW, Hickam DH, Elliot DL: A comparison of men and women physicians' management of patient death [Information]. West J Med 1985 Nov; 143:691-693)

From the Division of General Medicine, Department of Medicine, The Oregon Health Sciences University, Portland.

Reprints are not available.

Women reported slightly greater levels of personal anxiety following patient death, but the difference was not significant ($P = .2$). About 41% of men and 48% of women indicated that notifying the family of a death was usually or always difficult. Only 2% (two men and one woman) reported that death notification was never difficult. Physicians with fewer patient deaths reported greater personal anxiety, and this trend was equally true for both men and women.

Physician-initiated family contact following a patient's death was similar for women and men physicians (Table 2). Nearly all physicians (94%) indicated that they were usually or always available if the family called with questions. A phone call to the family after death was usually or always done by 20% of physicians. Less than a third of all respondents reported routinely initiating any form of family contact after a death. However, when an autopsy was done, 70% routinely contacted the family to discuss the findings. No significant difference between men and women physicians was observed in any form of reported contact after the family had been notified of the death.

Men and women physicians use similar methods to notify families of a loved one's death. All physicians frequently informed families by telephone, with 62% of men and 61% of women indicating that this was their usual practice. Families were informed in person at the hospital in 26% of the deaths, and a mixture of other methods was used to notify families in selected circumstances. When a death was unexpected, both sexes were more likely to notify the family in person, rather than by phone.

In studies that do not show a significant difference between two comparison groups, it is essential to calculate the probability of a type 2 statistical error.[8] We calculated this probability using published formulas for the comparison of proportions.[9] We have estimated that a clinically significant difference between men's and women's behavior of family notification would be that one gender primarily used the telephone in 60% of cases and the other gender used the telephone in 75%. Our sample size of 69 pairs allows a probability of .6 of detecting a difference of this magnitude.

Only one significant gender-associated difference in physician approach to patient death was identified, and this relates to an aspect of education rather than management. Women indicated a greater frequency of individual reading dealing with a dying patient ($P = .03$). Formal training in medical school, continuing medical education and religious training on death management did not vary with gender.

TABLE 1.—*Men and Women Physician Demographics*

Demographics	*Women N = 69*	*Men N = 69*
Age, yr	41.5 ± 10.2*	42.0 ± 10.0
Specialty, No. (%)		
General surgery	4 (6)	10 (14)
Family practice	17 (25)	21 (30)
General practice	7 (10)	6 (9)
Internal medicine	31 (45)	22 (32)
Obstetrics/gynecology	6 (9)	6 (9)
Other†	4 (6)	4 (6)
Number of patient deaths/year, No. (%)		
1	6 (9)	6 (9)
2 to 5	43 (62)	40 (58)
>6	20 (29)	23 (33)

*Standard deviation.
†"Other" are six physicians practicing in emergency rooms, one anesthesiologist and one dermatologist.

TABLE 2.—*Routine Practices of Physicians Following Patient Death*

	Women N = 69 Number (%)	*Men N = 69 Number (%)*	*P*
Available if family called	65 (94)	65 (94)	.8
Physician telephones the family	16 (23)	12 (17)	.7
Physician calls family with results of autopsy	47 (68)	50 (72)	.5
Physician sends a card or flowers or attends the funeral	14 (20)	7 (10)	.1
Physician schedules a follow-up office visit with the family	10 (14)	5 (7)	.2

Conclusions

Men and women physicians are similar in their reaction to patient death. We find no evidence that women physicians have increased personal contact, availability or follow-up with families after a loved one's death. The degree of reported physician anxiety in notifying the family of a death was similar for men and women. Physician-initiated subsequent family contact, whether by card, phone call or office appointment, was the routine practice of a few physicians and was not reported with greater frequency by women. Likewise, the methods of notifying the family following a death were the same, with both sexes indicating using the telephone as their usual means of family contact.

To determine differences between men and women physicians, we felt it important to control for demographic characteristics that have potential impact on the management of patient death: age, specialty distribution and number of patient deaths per year. Women physicians tend to be younger, and a greater percentage are in primary care specialties.[10,11] Physician age could possibly affect the management of patient death, as recent graduates are more likely to have been exposed to medical school training regarding death,[12] whereas older physicians are likely to have greater personal experience. Specialty may affect death management by altering the patient mix and the percentage of expected and unexpected deaths. We have previously documented that the number of deaths in one's practice influences physician anxiety and subsequent reaction to patient deaths.[5] As might be anticipated, physicians with fewer deaths indicate greater personal anxiety in dealing with patient death. Physicians' management of unexpected deaths is different from that in expected deaths.[13] In this study we matched our physician pairs for specialty and total deaths and quantitated the percentage of anticipated deaths to assure similarity.

The commonly held premise that women physicians are more compassionate is not supported by our matched data. We are unable to substantiate any gender-associated differences in handling any aspect of patient death. The only identified difference was that women report more individual reading on the care of a dying patient. Our sample size, although well matched, provides only moderate statistical

power to detect small differences. In addition, our survey instrument does not allow for qualifying the content of interactions, only their character and frequency. We have previously used this survey instrument, however, to show differences among provider groups.[5]

One explanation for this lack of difference is that the more nurturing tendencies attributed to women are due to demographic factors. Significant differences in men and women physicians have been well documented, particularly with regard to age and specialty distribution.[11] It may be that women physicians are, as a pool, more humane, but that, when matched for confounding factors, these differences disappear. When controlled for age, specialty and number of patient deaths, the reactions of men and women physicians to patient death are the same.

We have identified no practices of women physicians in death management to support the stereotype that women are more humane. There was no evidence of increased family contact, support or communication with families by women physicians following patient death. Our findings are in line with the American Medical Association's report that men and women in general spend a similar amount of time with patients, as indicated by the average length of an office visit (30.5 minutes for women and 31.6 minutes for men).[14] Perhaps Eisenberg is correct in asserting that "Women physicians more nearly resemble men physicians in professional attitudes than they do other women in the population."[15] She asserts that the powerful medical school selection process and subsequent socialization into medical roles result in greater similarities than differences in men and women physicians. Whatever the reasons, we find no evidence of increased humaneness in women physicians in their management of patient death. If family needs are to be better met at the time of patient death, increased sensitivity needs to be further developed in both male and female members of the medical profession.

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Health Problems of Agricultural and Forestry Workers

KENNETH W. KIZER, MD, MPH
Sacramento, California

AGRICULTURE AND FORESTRY are big businesses in the western United States. Indeed, agriculture is California's number one industry, and California is the leading producer of food and fiber in the United States. It is surprising, then, that relatively few investigations have focused on the health hazards of these industries, especially in view of the reported association of several types of cancer and infectious diseases with farming and the fact that these industries have work injury death rates nearly five times higher than the overall average occupational injury death rate.

Agricultural and forestry workers are at risk for a variety of unusual and serious injuries, most of which are due to farm machinery accidents. Tractors are the machines most often involved in these accidents, while grain augers and power takeoffs contribute to a disproportionate number of severe and permanently disabling injuries.[1] Amputations, crush injuries and compound fractures of the extremities; spinal cord injuries, and blunt trauma of the chest and abdomen are the most common serious injuries suffered by these workers, in addition to common lacerations, contusions and tendon and ligament injuries. Among the recently recognized injuries unique to agriculture is the hay balers' fracture—combined fractures of the sternum and T-12 vertebrae—that results when a bale of hay falls on the driver of a front-end-loading hay baler vehicle, causing severe forward flexion and consequent vertebral collapse at the dorsolumbar junction, along with fracture of the sternum from direct trauma against the steering wheel.[2]

Many of these machinery injuries could be prevented if automatic protective devices (such as safety shields, roll bars or protective cabs) and more stringent safety practices were incorporated into the design and use of such equipment.

Several characteristics of farming account for increased problems with trauma. These include (1) the family nature of much farming—that is, farm work is often undertaken by all members of a family, including the very young and the elderly, (2) agricultural workers perform a wide variety of tasks, in all kinds of weather and other environmental conditions and they usually work very long hours, seven days a week, during busy times of the year, (3) machinery is integral to most farming activities and much of this equipment is exempt from standards set by the Occupational Health and Safety Administration and (4) farmers often work alone and the agricultural work site is typically remote from medical facilities, both of which often cause delay in giving first aid and medical assistance to an injured worker.

Nontraumatic health hazards are also of special concern in agriculture and forestry. Several studies have reported in-

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creased relative frequencies of melanoma and other skin cancers, leukemia, non-Hodgkin's lymphoma, multiple myeloma, brain neoplasms and prostate cancer among workers in these industries.[3-5] Whether pesticides, herbicides, fumigants, fertilizers and other agricultural chemicals, including natural toxic gases such as nitrogen dioxide and hydrogen sulfide, to which these workers are exposed have an etiologic role in these types of cancer is unknown, although acute illnesses resulting from exposure to such toxic chemicals are well recognized.

Higher rates of skin infections, tuberculosis and other infectious diseases also typify these occupations. Illustrative of the peculiar infectious diseases that afflict agricultural workers is the recent multistate outbreak of cutaneous sporotrichosis that resulted from exposure to prairie hay.[6] Further, the increasingly frequent discovery of antimicrobial drug-resistant pathogens resulting from adding subtherapeutic amounts of antibiotics to farm animal feeds raises particular concerns about infectious diseases occurring in these workers.[7]

Although results of various studies on the health problems of agricultural and forestry workers are generally less than conclusive and, at times, conflicting, sufficient data do exist to indicate the need for further investigation into agricultural accidents, in particular, and other health problems identified with these very important industries.

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In Memoriam

Arizona Medical Association

BRADSHAW, ALFRED KENNETH, Tempe. Died June 29, 1985, aged 63. Graduate of the University of Alberta Faculty of Medicine, Edmonton, 1946. Licensed in Arizona in 1981. Dr Bradshaw was an associate member of the Maricopa County Medical Society.

DAVIS, LEE P., Phoenix. Died June 29, 1985, aged 51. Graduate of Ohio State University College of Medicine, Columbus, 1960. Licensed in Arizona in 1962. Dr Davis was a member of the Maricopa County Medical Society.

MELICK, DERMONT W., Phoenix. Died July 20, 1985, aged 75. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1935. Licensed in Arizona in 1936. Dr Melick was a member of the Maricopa County Medical Society.

SMITH, CHARLES S., Nogales. Died May 31, 1985, aged 92. Graduate of Emory University School of Medicine, Atlanta, 1914. Licensed in Arizona in 1927. Dr Smith was a member of the Santa Cruz County Medical Society.

WAGNER, ALBERT G., Phoenix. Died July 19, 1985, aged 76. Graduate of the University of Illinois College of Medicine, Chicago, 1942. Licensed in Arizona in 1957. Dr Wagner was a member of the Maricopa County Medical Society.

California Medical Association

BORDERS, DONALD D., Fresno. Died April 3, 1985, aged 53. Graduate of Duke University School of Medicine, Durham, NC, 1958. Licensed in California in 1967. Dr Borders was a member of the Fresno-Madera County Medical Society.

BROCHARD, VICTOR P., San Francisco. Died February 23, 1985, aged 74. Graduate of Université de Paris Faculté de Médecine, 1936. Licensed in California in 1948. Dr Brochard was a member of the San Francisco Medical Society.

GORDON, CHARLES ROY, Sacramento. Died April 26, 1985, aged 41. Graduate of Louisiana State University School of Medicine, New Orleans, 1968. Licensed in California in 1971. Dr Gordon was a member of the Sacramento-El Dorado Medical Society.

HAND, HAROLD E., San Francisco. Died July 30, 1985, in Palo Alto, aged 83. Graduate of Creighton University School of Medicine, Omaha, 1928. Licensed in California in 1928. Dr Hand was a retired member of the San Francisco Medical Society.

HOVSEPIAN, DERON, Pasadena. Died April 15, 1985, aged 69. Graduate of the University of Southern California School of Medicine, Los Angeles, 1941. Licensed in California in 1941. Dr Hovsepian was a member of the Los Angeles County Medical Association.

JARES, JOHN JAMES, Jr, West Los Angeles. Died April 24, 1985, in Santa Monica, aged 77. Graduate of the University of Rochester School of Medicine and Dentistry, 1935. Licensed in California in 1944. Dr Jares was a member of the Los Angeles County Medical Association.

KOZAK, PETER P., Jr, Orange. Died August 5, 1985, of myocardial infarction, aged 50. Graduate of St Louis University School of Medicine, 1960. Licensed in California in 1962. Dr Kozak was a member of the Orange County Medical Association.

PRATUM, LEIF KROGH, Rancho Mirage. Died December 18, 1984, aged 62. Graduate of the University of Louisville School of Medicine, 1946. Licensed in California in 1960. Dr Pratum was a member of the Riverside County Medical Association.

VELARDE, ALBERT L., San Leandro. Died July 9, 1985, in San Leandro, aged 74. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1940. Licensed in California in 1940. Dr Velarde was a member of the Alameda-Contra Costa Medical Association.

WATTERS, LORRAIN E., Jr, Sacramento. Died November 11, 1984, aged 62. Graduate of State University of Iowa College of Medicine, Iowa City, 1946. Licensed in California in 1955. Dr Watters was a member of the Sacramento-El Dorado Medical Association.

WILLIAMS, HAROLD MCNEAL, Fresno. Died February 9, 1985, aged 53. Graduate of Howard University College of Medicine, Washington, DC, 1958. Licensed in California in 1963. Dr Williams was a member of the Fresno-Madera Medical Society.

YARDLEY, JACK M., Roseville. Died April 26, 1985, aged 60. Graduate of Columbia University College of Physicians and Surgeons, New York, 1956. Licensed in California in 1962. MD degree from California College of Medicine, 1962. Dr Yardley was a member of the Placer-Nevada County Medical Association.

New Mexico Medical Society

JONES, CHARLOTTE A., Santa Fe. Died September 13, 1985, aged 80. Graduate of Long Island College of Medicine, New York, 1934. Licensed in New Mexico in 1947. Dr Jones was an Emeritus member of the Santa Fe County Medical Society.

Utah State Medical Association

JENSON, HAROLD S., Farmington. Died August 19, 1985, in Bountiful, aged 70. Graduate of Rush Medical College, Chicago, 1942. Licensed in Utah in 1943. Dr Jenson was a member of the Davis County Medical Society.

WARENSKI, LEO CARL, Salt Lake City. Died July 7, 1985, in Salt Lake City, aged 86. Graduate of Washington University School of Medicine, St Louis, 1925. Licensed in Utah in 1926. Dr Warenski was a member of the Salt Lake County Medical Society.

Wyoming Medical Society

EWING, CHARLES W., Casper. Died September 2, 1985, in Ogden, Utah, of injuries received in plane crash, aged 54. Graduate of the University of Texas Branch, Galveston, 1962. Licensed in Wyoming in 1981. Dr Ewing was a member of the Natrona County Medical Society.

Book Reviews

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

PRETERM BIRTH: CAUSES, PREVENTION, AND MANAGEMENT—Edited by Fritz Fuchs, MD, Professor of Obstetrics and Gynecology, Cornell University Medical College, and Attending Obstetrician and Gynecologist, The New York Hospital, and Phillip G. Stubblefield, MD, Associate Professor of Obstetrics and Gynecology, Harvard Medical School, Boston, and Chairman, Department of Obstetrics and Gynecology, Mt Auburn Hospital, Cambridge, Mass. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1984. 376 pages, $48.

This much-needed book elegantly addresses the causes, prevention and management of preterm birth in light of our current knowledge. It also offers the reader a glimpse into potential future developments in the field. Dr Stubblefield offers an excellent overview at the beginning of the book and each of the authors reviews his or her separate topic in significant detail so that the reader may grasp not only the current stage of our knowledge and understanding of the specific topic, but also derive an understanding for directions that current research is taking. Most of the chapter authors are renowned experts in their individual areas. There are fine reviews of the social and personal factors related to preterm birth as well as the role of infection. Each of the specific pharmacologic approaches to preventing preterm labor is discussed. I particularly enjoyed the chapters by Creasy and Katz and Grospietsch and Kuhn on β-adrenergic tocolytics, and the review by Johnson and Dubbins of progestins and gamissans and Balasch's review on prostaglandin synthetase inhibitors since each of these groups of compounds singularly and in combination are rapidly becoming our first line of attack in these problems.

The book also discusses the social implications of preterm labor and the impact of regional organization and planning in order to offer services to reduce perinatal mortality.

The text is a complete and detailed review of the subject and, as such, should be of value to students, residents, fellows and practicing physicians. The style is easy to read and the material is presented in a concise and logical fashion. The references are extensive and should satisfy any reader who wishes to broaden his knowledge in this area.

Since our knowledge of the causes, prevention and management of preterm birth is growing and developing rapidly, I would imagine the authors will need to update this text frequently. If they do, they will offer a much needed service to the profession.

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* * *

NEUROMUSCULAR MANIFESTATIONS OF SYSTEMIC DISEASE—in the CONTEMPORARY NEUROLOGY Series—Robert B. Layzer, MD, Professor of Neurology, University of California, San Francisco, School of Medicine. F. A. Davis Co, 1915 Arch St, Philadelphia, PA 19103, 1984. 409 pages, $60.00.

This is the latest volume in the Contempory Neurology Series and like its predecessors it is authoritative and quite readable. The title of this volume suggests that it is directed toward practicing neurologists, but it would equally serve as a valuable resource for specialists who take care of patients in whom disorders of the neuromuscular system develop as a result of systemic illness.

The book is well organized, the first chapter being devoted to a general clinical and diagnostic approach to neuromuscular symptoms and disease. Especially valuable is the conservative approach taken as to the value of muscle and nerve biopsy. Each of the next nine chapters are devoted to those neuromuscular complications that accompany a specific group of systemic illnesses: "Mineral and Electrolyte Disorders," "Endocrine Disorders," "Infection," "Inflammatory and Immune Disorders," "Neoplastic Diseases," "Renal Disorders," "Circulatory Disorders," "Nutritional and Gastrointestinal Disorders" and "Complications of Medical and Surgical Treatment." Each chapter is more than adequately documented with very recent references. The author has obviously had a great deal of experience with neuromuscular disorders and he successfully uses his personal experience to help clarify some of the controversial information reported in the recent literature.

To this reviewer's knowledge this is the first book devoted to the important clinical topic of neurologic complications of systemic illness since Dr Aita's book which is very outdated. One would hope that the editors of the Contemporary Neurology Series would develop a companion volume, equal in quality to this volume, that would cover the central nervous system complications of systemic illness.

This book is highly recommended for practicing neurologists and other medical specialists. It probably should be required reading for neurology residents and certainly should be available in hospital libraries for medical and surgical residents to use as a valuable resource book.

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* * *

SKIN PROBLEMS OF THE AMPUTEE—S. William Levy, MD, Research Associate, Biomechanics Laboratory, and Clinical Professor of Dermatology, University of California, San Francisco. Warren H. Green, Inc, 8356 Olive Blvd, St Louis, MO 63132, 1983. 304 pages, $39.95.

This text reflects the remarkable experience of a dedicated dermatologist who has been specifically concerned for nearly a third of a century about skin problems of amputees. The introductory chapter provides basic information regarding lower limb dynamics and the structure and function of skin as this relates to an amputee, the residual limb and the prosthesis that will allow substitute function. The remainder of the text is directed toward the effect of the prosthetic interface as it relates to the skin and the pathological states seen among the thousands of amputees Dr Levy has had the opportunity to examine, observe and treat. The last section covers the practical aspects of treatment of the skin disorders which develop.

The man/machine interface is critical to wearing an inert prosthetic substitute for limb loss. Every amputee who wears a prosthesis experiences the skin adaptations and problems incident to this intimate interface. Much of the skin involving the interface is not designed physiologically to undergo the environment and the variety of pressures inherent in prosthetic wearing. This text is an excellent overview and summary of the influence of that environment on the skin as an organ.

The author is to be congratulated for his diligence and for his contribution to an otherwise largely neglected area of dermatology. The text is well illustrated and nicely printed. It should be command reading and available as a reference for all members of the amputee team including the surgeon, the rehabilitationist, the prosthetist and others involved in amputee management. Many amputees themselves would benefit by reading this text.

The wide availability of newer synthetic materials, particularly composite plastics, will further create environmental changes in the prosthetic/skin interface. Dr Levy could have further elaborated on the response to some of the newer materials. This is covered in his text but not specifically in relation to the present research trends in prosthetic materials. Perhaps the second edition of this fine and timely text will extend more completely into the area of new materials and the response of the skin to this unique contact environment.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

COMPREHENSIVE MANAGEMENT OF RESPIRATORY EMERGENCIES—Edited by Barry E. Brenner, MD, PhD, Assistant Director, Emergency Medicine Center, UCLA Hospital and Clinics, and Assistant Professor of Medicine, UCLA Center for Health Sciences, Los Angeles. Aspen, 1600 Research Blvd, Rockville, MD 20805, 1985. 386 pages, $61.50.

CURRENT SURGICAL DIAGNOSIS & TREATMENT—Seventh Edition—Edited by Lawrence W. Way, MD, Professor of Surgery, University of California, San Francisco, School of Medicine; Chief of Surgical Service, Veterans Administration Medical Center, San Francisco; illustrated by Laurel V. Schaubert. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1985. 1,226 pages, $31.50 (softbound).

DRG SURVIVAL MANUAL FOR THE CLINICAL LAB—Edited by Robert J. Fitzgibbon, Editor, *MLO/Medical Laboratory Observer,* and Bernard E. Statland, MD, PhD, Director of Laboratory Medicine, Professor of Pathology and Medicine, Boston University Medical Center. Medical Economics Books, Oradell, NJ 07649, 1985. 264 pages, $19.95 (soft cover).

THE ECONOMICS AND POLITICS OF HEALTH—Revised Edition—Rita Ricardo-Campbell, PhD, Senior Fellow, Hoover Institution, Stanford University, Stanford, California. The University of North Carolina Press, PO Box 2288, Chapel Hill, NC 27514, 1982. 366 pages, price not given (paperback).

EMERGENCY PROBLEMS IN THE ELDERLY—Edited by Edward P. Hoffer, MD, FRCP(C), Associate Professor of Medicine, University of Massachusetts Medical School, Worcester; Lecturer in Medicine, Harvard Medical School, Boston, and Director of Pre-Hospital Care, Framingham Union Hospital, Framingham, Massachusetts. Medical Economics Books, 680 Kinderkamack Rd, Oradell, NJ 07649, 1985. 240 pages, $22.95.

EXPLORING NEW VISTAS IN HEALTH CARE—Edited by John M. Virgo, Atlantic Economic Society, International Health Economics and Management Institute, Southern Illinois University at Edwardsville; Foreword by C. Everett Koop, Surgeon General, United States Public Health Services. International Health Economics and Management Institute, Box 101, Southern Illinois University at Edwardsville, Edwardsville, IL 62026, 1985. 341 pages, $25, US and Canada; $30, overseas (paperback).

MAXILLOFACIAL INJURIES—2 Volumes—N. L. Rowe, CBE, FRCS(Eng), FDSRCS(Eng), Hon. FDSRCS(Edin), Hon. FDSRCPS(Glasg), Hon. FFDRCS(Irel), Honorary Consultant in Oral and Maxillofacial Surgery to the Westminister Hospital, London, and Queen Mary's Hospital, Roehampton, UK, and J. L1. Williams, MB, BS, BDS, FDSRCS(Eng), LRCP(Lond), MRCS(Eng), Consultant Oral and Maxillofacial Surgeon, South West Thames Regional Health Authority, and Honorary Consultant Oral and Maxillofacial Surgeon, Queen Mary's Hospital, Roehampton, and King Edward VII Hospital, Midhurst, Sussex, UK. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 1,014 pages, $195.

MIGRAINE—UNDERSTANDING A COMMON DISORDER—Oliver Sacks, MD, Professor of Clinical Neurology, Albert Einstein College of Medicine, New York. University of California Press, 2120 Berkely Way, Berkeley, CA 94720, 1985. 257 pages, $17.95.

PEDIATRIC EMERGENCIES—Volume 7 in Clinics in Emergency Medicine—Edited by Stephen Ludwig, MD, Associate Professor of Pediatrics, University of Pennsylvania School of Medicine; Director, Emergency Department, Children's Hospital of Philadelphia, and Educational Coordinator, Supportive Child Adult Network, Inc, Philadelphia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 256 pages, $35.

PLAY SAFE—HOW TO AVOID GETTING SEXUALLY TRANSMITTED DISEASES—Bea Mandel and Byron Mandell. Center for Health Information, PO Box 4636, Foster City, CA 94404, 1985. 98 pages, $4.95 (paperback).

PREMENSTRUAL SYNDROME—A CLINIC MANUAL—H. Jane Chihal, MD, PhD, Texas Endocrine and Fertility Institute, Carrollton, Texas. Creative Infomatics, Inc, PO Box 1607, Durant, OK 74702-1607, 1985. 149 pages, price not given (softbound).

RADIONUCLIDE IMAGING OF THE BRAIN—Volume 1 in Contemporary Issues in Nuclear Imaging—Edited by B. Leonard Holman, MD, Professor of Radiology, Harvard Medical School, and Director, Clinical Nuclear Medicine Service, Brigham and Women's Hospital, Boston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 223 pages, $55.

THE RESIDENT'S FRIEND—BETTER PATIENT CARE THROUGH COMPUTING—An information management program for medical students, interns, residents, and fellows on Apple™-type computers—Bruce I. Rose, PhD, MD, Stanford University Hospital, Stanford, California. BYTE-OMEGA, 695 Torrington Drive, Sunnyvale, CA 94087, 1984. This software package contains two program disks, warranty card and manual and is available for $99 + $3 shipping + (applicable California) tax.

REVIEW OF MEDICAL PHYSIOLOGY—12th Edition—William F. Ganong, MD, Jack and DeLoris Lange Professor of Physiology, and Chair, Department of Physiology, University of California, San Francisco. Lange Medical Publications, Los Altos, CA 94023, 1985. 654 pages, $22.50.

SCIENTIFIC BASIS OF OBSTETRICS AND GYNAECOLOGY—Edited by Ronald R. Macdonald, MD, FRCS(Ed), FRCOG, Consultant Obstetrician and Gynaecologist, The Hospital for Women and Children, The General Infirmary, and Senior Clinical Lecturer in Obstetrics and Gynaecology, University of Leeds, United Kingdom. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 514 pages, $59.

SEPTIC SHOCK—Volume 4 in Contemporary Issues in Infectious Diseases—Edited by Richard K. Root, MD, Professor and Vice Chairman, Department of Medicine, University of Washington School of Medicine, and Chief, Medical Service, Seattle Veterans Administration Medical Center, Seattle, and Merle A. Sande, MD, Professor and Vice Chairman, Department of Medicine, University of California, San Francisco, School of Medicine, and Chief, Medical Service, San Francisco General Hospital. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 276 pages, $42.

TEXTBOOK OF ANAESTHESIA—Edited by G. Smith, BSc, MD, FFARCS, Professor of Anaesthesia, and A. R. Aitkenhead, BSc, MB, ChB, FFARCS, Senior Lecturer in Anaesthesia, University of Leicester School of Medicine, Leicester, UK. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 564 pages, $36 (paperback).

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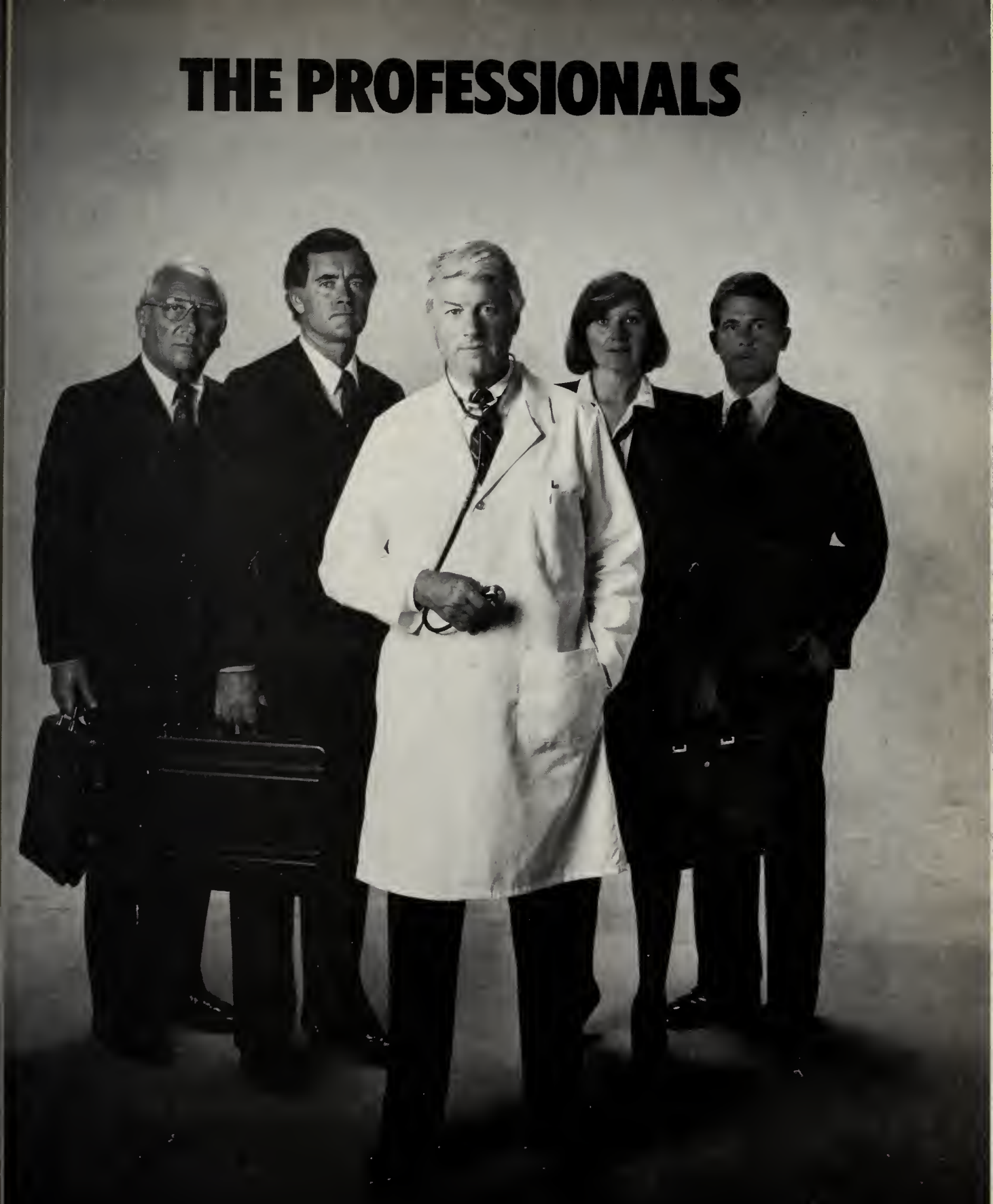

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INTERNIST with sub-speciality to join six established in Mountain View, California. Near 450 bed, well equipped hospital and Stanford University. Send CV to El Camino Internal Medical Group, Inc., 125 South Dr., Mountain View, CA 94040.

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KETCHUM, SUN VALLEY, IDAHO: Internist, OB/GYN, Pediatrician, Orthopedist in multispecialty, expanding, well-equipped clinic. Income moderate; quality of life highest. Dr Bryan Stone, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

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OBSTETRICIAN-GYNECOLOGIST—Personable and industrious female Obstetrician-Gynecologist desired to join 3-physician department in 28-physician multispecialty group. Immediate practice opportunity. Drawing area 185,000. Western slope of the Rockies. Excellent hospital facilities. Superb living conditions. Unexcelled skiing and outdoor recreation. Primary fee-for-service. HMO option. Please send curriculum vitae and references to Mary Beard, MD, Ogden Clinic, 4650 Harrison, Ogden, UT 84403.

FAMILY PRACTITIONER—Tulare County, California. Board certified/eligible Family Practitioner to practice in an outpatient clinic, which includes inpatient duties, with 13 physicians. Consider a semi-rural lifestyle with cultural amenities, the Coast and the Sierra Nevada Mountains easily accessed. Salary: $81,236 to $85,376 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. An Affirmative Action Employer.

OB/GYN—Tulare County, California. Board certified/eligible OB/GYN to practice in an outpatient clinic, which includes inpatient duties, with 13 physicians. Consider a semi-rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $88,837 to $93,365 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. An Affirmative Action Employer.

INTERNIST or internal medicine subspecialist to associate with recently established Internist/Rheumatologist in growing Northern California community of 150,000. Incentives offered. Reply with CV to Rex Adams, MD; PO Box 5375, Modesto, CA 95352-5375.

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(Continued on Page 702)

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(Continued from Page 700)

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PROGRESSIVE MULTISPECIALTY GROUP of 29 physicians needs Family Practitioner. New building adjacent to modern, well-staffed hospital in excellent medical community. $55,000 salary plus bonus first year. Full stockholder status thereafter plus many fringe benefits. Close to excellent hunting, fishing and skiing. Town of 25,000 in agricultural area 20 miles from state capitol. Contact: M. Crane, 215 E. Hawaii, Nampa, ID 83651; (208) 467-1121.

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OPPORTUNITY AVAILABLE for Family Practice physician interested in surgery and OB in group practice in desirable rural area. Clinic and hospital well-equipped. Call/write F. L. Nutter, Administrator, 1101 Texas, Deer Lodge, MT 59722; 1 (406) 846-2212.

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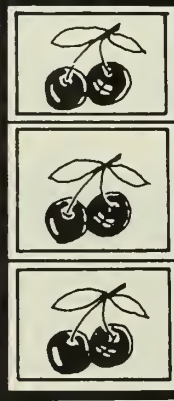

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The Western Journal of Medicine

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION as required by the Act of August 12, 1970; Section 3685, United States Code, for **THE WESTERN JOURNAL OF MEDICINE,** published monthly at San Francisco, California, for October 1985.

1. Location of known office of publication: 44 Gough Street, San Francisco, California 94103.

2. Location of the headquarters or general business office of the publisher: 44 Gough Street, San Francisco, California 94103.

3. Publisher: California Medical Association, 44 Gough Street, San Francisco; Editor, Malcolm S. M. Watts, M.D., 44 Gough Street, San Francisco; Managing Editor, David Greer, 44 Gough Street, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 44 Gough Street, San Francisco, California (an unincorporated association).

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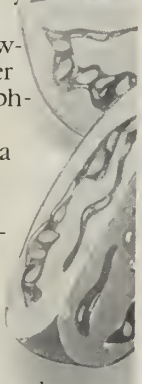
There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.



Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash, and tomatoes, citrus fruits and brussels sprouts.

Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

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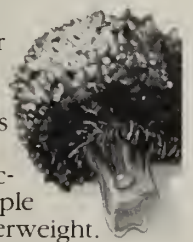

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Long Beach	Oct. 24, 1985	Hyatt Edgewater • 6400 E. Pacific Coast Hwy.
Anaheim	Oct. 25, 1985	Sheraton Anaheim Motel • 1015 W. Ball Rd.
San Diego	Nov. 5, 1985	Holiday Inn at the Embarcadero • 1355 N. Harbor Dr.
Torrance	Nov. 6, 1985	Holiday Inn-Torrance • 21333 Hawthorne Blvd.
Pasadena	Nov. 7, 1985	Holiday Inn of Pasadena • 303 E. Cordova St.
San Francisco	Nov. 19, 1985	Westin St. Francis • 335 Powell St. & Union Square
Sacramento	Nov. 20, 1985	Holiday Inn-Holidome • 5321 Date Ave.
Marina Del Rey	Nov. 21, 1985	Marina International Hotel • 4200 Admiralty Way
Orange County	Nov. 22, 1985	Weston South Coast Plaza • 666 Anton Blvd.
Palo Alto	Dec. 2, 1985	Hyatt Rickeys • 4219 El Camino Real
Fresno	Dec. 3, 1985	Ramada Inn • 324 E. Shaw Ave.
Stockton	Dec. 4, 1985	The Stockton Hilton • 2323 Grand Canal Blvd.
Los Angeles	Dec. 5, 1985	Hyatt on Sunset • 8401 Sunset Blvd.
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Sacramento	Mar. 4, 1986	Ramada Inn • 1900 Canterbury Road
San Francisco	Mar. 5, 1986	San Francisco Airport Hilton • Intern'l. Airport
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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: June 5-7, 1986, Loews Ventana Canyon Resort, Tucson.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1986: date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1986: date and place to be announced.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1986: date and place to be announced.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1986: date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 2-4, 1986, Winnemucca.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Interim Meeting: November 15-16, 1985, Holiday Inn de Las Cruces, Las Cruces. Centennial Meeting: April 30-May 2, 1986, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 25-27, 1986, Valley River Inn, Eugene.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1986: date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: 1986: date and place to be announced.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1986, Jackson Lake Lodge, Moran.

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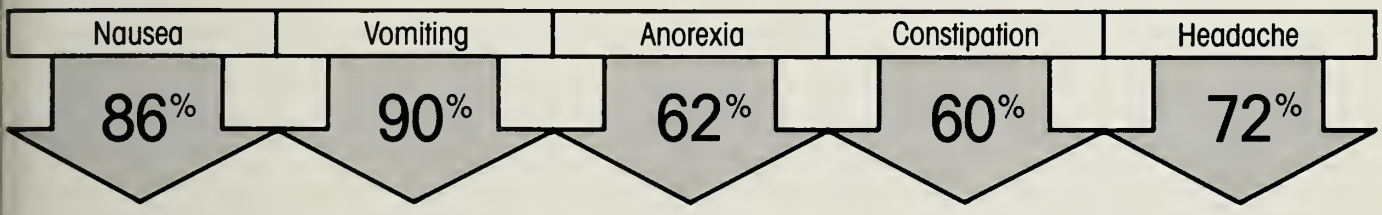

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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Feighner JP, *et al Psychopharmacology 61*:217-225, Mar 22, 1979

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

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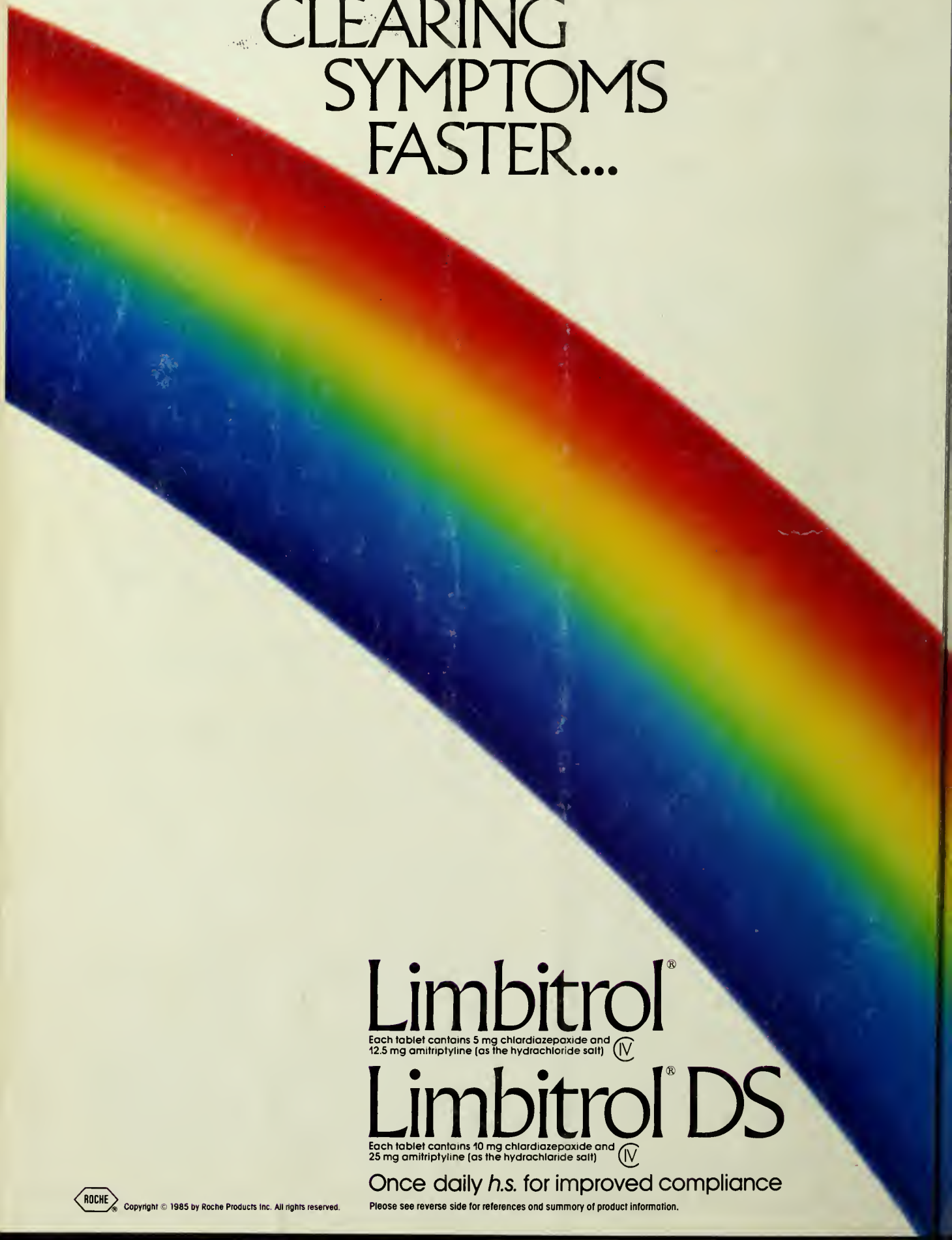

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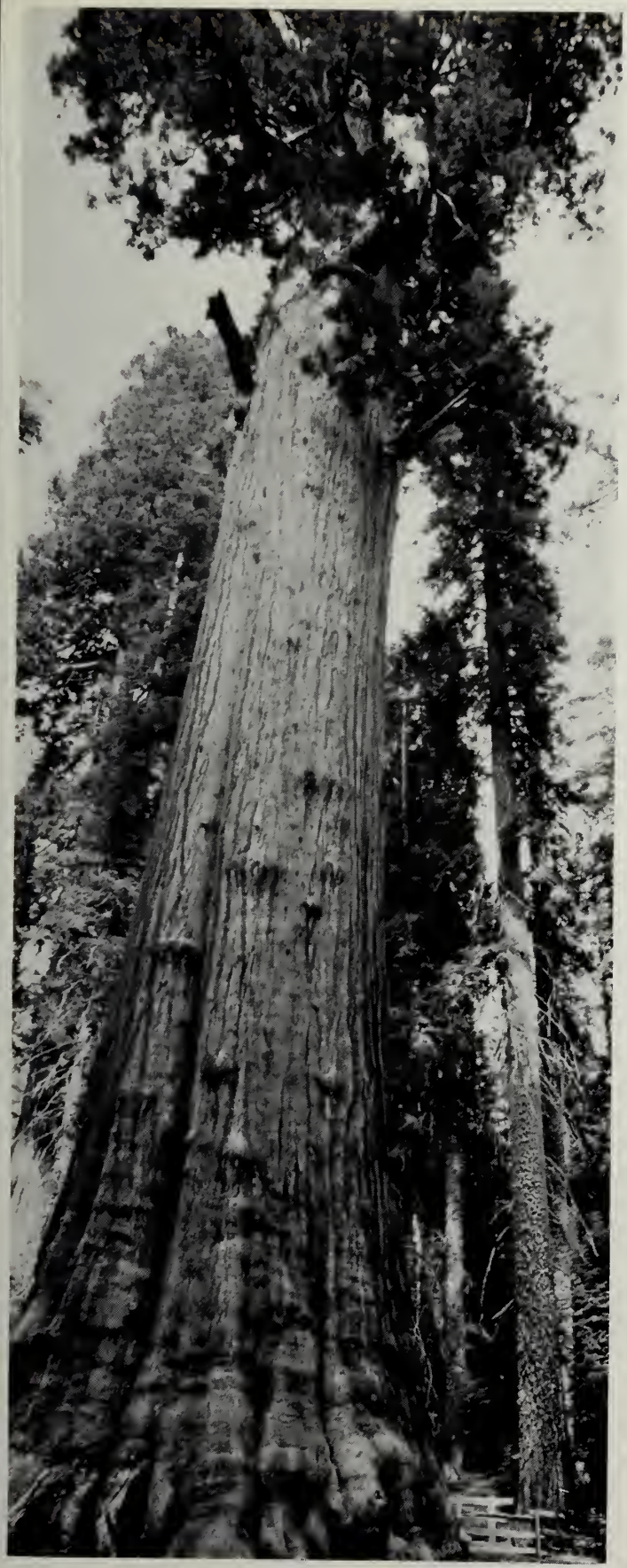

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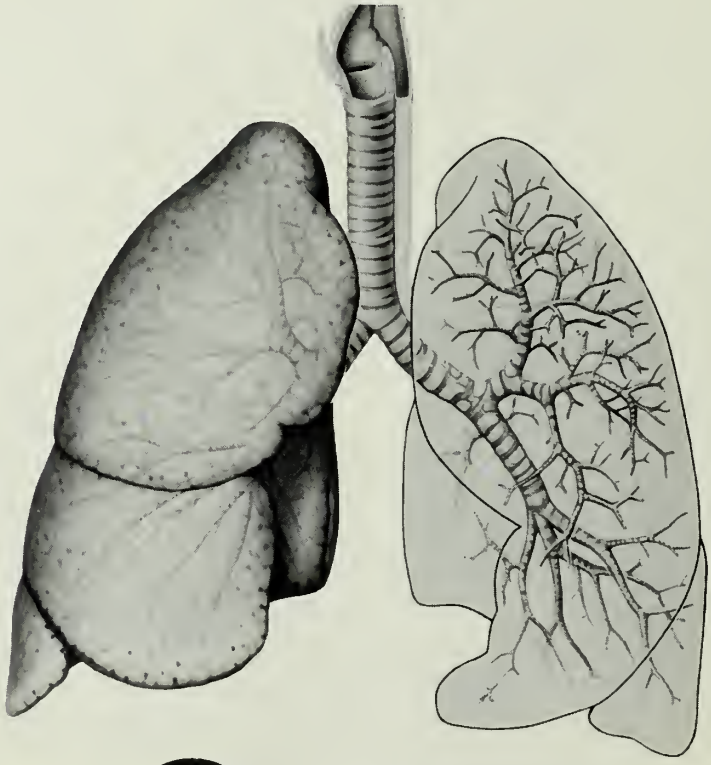

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Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* Other causes of colitis should be ruled out

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly) There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0 18, 0 20, 0 21, and 0 16 mcg/ml at two, three, four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor is administered to a nursing woman

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note. Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information

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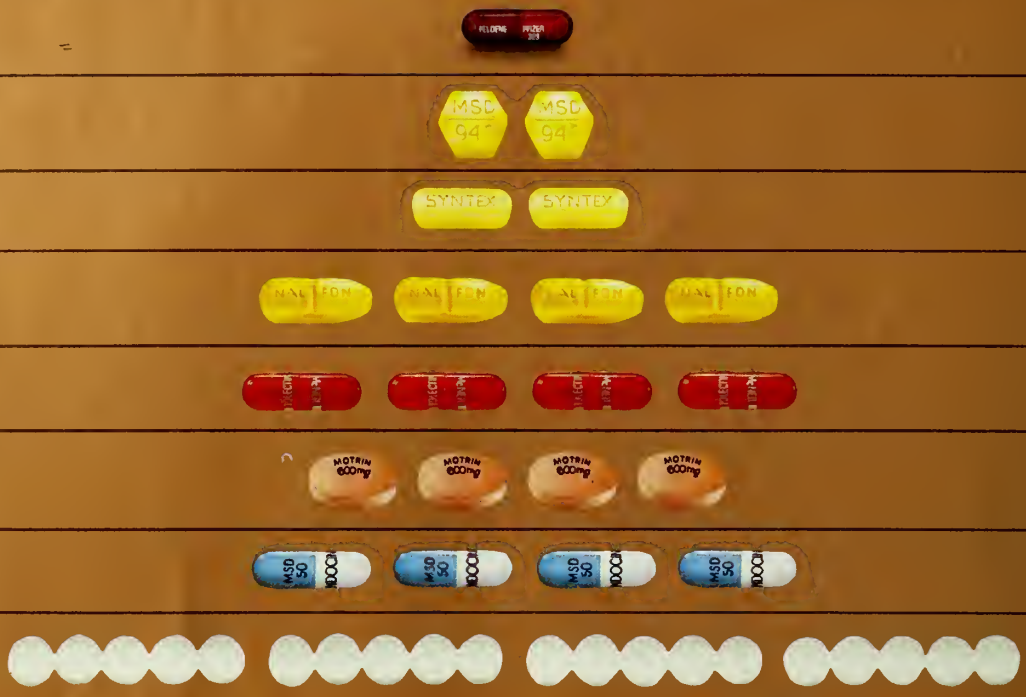

Source: PDR, 1985; Manufacturers' Prescribing Information

Indicates maximum dosage for osteoarthritis and rheumatoid arthritis for the antiarthritic agents included. Consult manufacturers' prescribing information.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome compnsed of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuna, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Because of extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE (piroxicam) at doses of 20 mg/day.

Incidance Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenital: BUN and creatinine elevations (see PRECAUTIONS)

Body as a Whole: headache, malaise

Special Senses: tinnitus

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

* Reactions occurring in 3% to 9% of patients treated with FELDENE

Reactions occurring in 1% to 3% of patients are unmarked.

Incidance Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Special Senses: swollen eyes, blurred vision, eye irritations

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

Incidance Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis

Dermatologic: onycholysis, loss of hair

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias

Urogenital System: dysuria

Body as a Whole: weakness

Cardiovascular/Respiratory: palpitations, dyspnea

Hypersensitivity: positive ANA

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis: It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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References: 1. Siegmeth W: Serum concentrations of piroxicam in relation to its clinical effect in patients with chronic polyarthritis (trans) *Wien Med Wochenschr* 130:31-35, 1980. 2. Tausch: Placebo-controlled study of piroxicam in the treatment of rheumatoid arthritis. *Am J Med* (report) 72:18-22, February 16, 1982. 3. Buxbaum J, Cronstein B: Efficacy of once-daily nonsteroidals in refractory rheumatoid arthritis patients. Presented as a scientific exhibit at the 77th Annual Scientific Assembly of the Southern Medical Association, Baltimore, November 6-9, 1983.

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SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg, for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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See following page.

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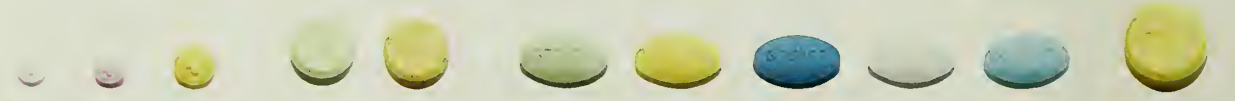

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5 mg 10 mg
Chewable Tablets

5 mg 10 mg 20 mg 30 mg 40 mg
Oral "Swallow" Tablets

40 mg
Sustained Action "Swallow" Tablets

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See previous page for brief summary of prescribing information.

The Western Journal of Medicine

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Cover illustration by Clifford S. Spohn

"With [CAPOTEN® (captopril tablets)] it appears that for the first time ever a patient can feel as well on treatment for high blood pressure as he does off it."[1]

*Angiotensin Converting Enzyme

†**CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

‡**The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

Reference:

1. Stumpe KO, Overlack A, Kolloch R, et al: Long-term efficacy of angiotensin-converting-enzyme inhibition with captopril in mild-to-moderate essential hypertension. Br J Clin Pharmacol 14(suppl 2):121S-126S, 1982.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine < 1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on Ist morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the Ist hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least I hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the Ist 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about I of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about I of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets.
(J3-658C)

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From the Division of Radiological Sciences, Department of Radiology, University of Colorado School of Medicine, Denver. Dr Hendee is now Assistant Vice-President for Science and Technology, American Medical Association, Chicago.

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STUART W. JAMIESON, MD, FRCS

From the Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, California.

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Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

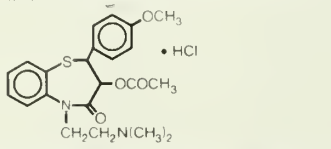
Please see full prescribing information on following page.

PROFESSIONAL USE INFORMATION

Cardizem® (diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CAROIZEM.
2. Exertional Angina: CAROIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CAROIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CAROIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CAROIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CAROIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CAROIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CAROIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CAROIZEM is indicated in the management of chronic stable angina. CAROIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CAROIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CAROIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CAROIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and AOVERSE REACTIONS.)

PRECAUTIONS

General. CAROIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CAROIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CAROIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CAROIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CAROIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LOH.
Oermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted.

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CAROIZEM.

The following postmarketing events have been reported infrequently in patients receiving CAROIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LOH, and CPK. However, a definitive cause and effect between these events and CAROIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CAROIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Oegree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LO_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LO_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Oosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CAROIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CAROIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NOC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CAROIZEM 60-mg scored tablets are supplied in bottles of 100 (NOC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NOC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 15—**Organ Transplants.** Pima County Medical Society Building, Tucson. Wednesday. Contact: ArMA.

January 17-19—**12th Annual Sports Medicine Symposium.** Holiday Inn Metrocenter, Phoenix. Friday-Sunday. Contact: ArMA.

February 13-15—**Them Ol' Bones.** Scottsdale Hilton Hotel, Scottsdale. Thursday-Saturday. Contact: St. Luke's Medical Center, (602) 251-8402.

February 19—**Urology-Including New Treatment Methods.** ArMA Building, Phoenix. Wednesday. Contact: ArMA.

February 21-23—**Anesthesia for the 80's.** Sheraton Scottsdale Resort, Scottsdale. Friday-Sunday. Contact: Arizona Society of Anesthesiologists, (602) 246-8901.

February 24-26—**Emergency Care Update VIII.** University of Arizona, Tucson. Monday-Wednesday. Contact: U of A.

February 24-27—**Practical Radiology: MRI, CT, Intervention, Computers and More.** Loews Ventana Canyon Resort, Tucson. Monday-Thursday. Contact: U of A.

February 26-28—**Ninth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wednesday-Friday. Contact: Phoenix OB/GYN Society, (602) 241-1917.

February 26-March 1—**International Ophthalmic Surgery Symposium.** Loews Paradise Valley Resort, Scottsdale. Wednesday-Saturday. Contact: The Eye Foundation, (602) 257-1077.

February 27-March 1—**Current Issues in Neurology and Neurosurgery.** La Posada Resort, Phoenix. Thursday-Saturday. Contact: Barrow Neurological Institute, (602) 285-3000.

March 6-8—**Focus '86.** Doubletree Inn, Scottsdale. Thursday-Saturday. Contact: St. Luke's Medical Center, (602) 251-8402.

March 8—**Rehabilitation and Aging.** Holiday Inn Broadway, Tucson. Saturday. Contact: U of A.

March 9-11—**Abuses and Controversies in Athletics and Exercise.** Tucson. Sunday-Tuesday. Contact: U of A.

March 18-21—**Pediatric Update 1986.** La Posada Resort, Scottsdale. Tuesday-Friday. Contact: Phoenix Children's Hospital, (602) 239-4350.

March 19—**Alternative Delivery Systems.** ArMA Building, Phoenix. Wednesday. Contact: ArMA.

March 20-22—**22nd Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thursday-Saturday. Contact: U of A.

March 22-23—**12th Annual James H. McDonald Urological Seminar.** Sheraton Scottsdale Resort, Scottsdale. Saturday-Sunday. Contact: Department of Surgery, Maricopa Medical Center, (602) 267-5371.

March 24-26—**Practical Cardiology for the Family Physician.** La Posada Resort, Scottsdale. Monday-Wednesday. Contact: American College of Cardiology, (301) 897-5400.

April 16—**Geriatrics.** ArMA Building, Phoenix. Wednesday. Contact: ArMA.

April 17—**Geriatrics.** VA Medical Center, Prescott. Thursday. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona-Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 95724. (602) 626-6173.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

(Continued on Page 730)

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Gastroenterology with endoscopy and ERCP, board certified	6,773
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Family Practice — minor surgery or assisting at surgery	6,773
Family Practice — major surgery	14,991
General Surgery	14,991
Internal Medicine with invasive vascular procedures	9,153
Internal Medicine — no invasive vascular procedures	4,393
Neurology	2,012
Ophthalmology with surgery or laser	6,773
Orthopedics with spinal surgery	18,449
Orthopedics — no spinal surgery	16,719
Otolaryngology— doing plastic surgery, board certified	14,991
Pediatrics — General	2,012
Pediatrics — General, with invasive vascular procedures	9,153
Plastic Surgery, board certified	14,991
Psychiatry — no electro-convulsive therapy	2,012
Radiology — diagnostic, no coronary angiography	4,393
Radiology — including coronary angiography	9,153
Urology	11,533

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ALLERGY AND IMMUNOLOGY

December 26-30—**Allergy, Drugs, and Drug Allergies.** Symposium Maui, Inc. and Hawaii Medical Association at Hawaii. Thursday-Monday. Contact: Joe Harrison, MD, Program Director Symposium Maui, PO Box 10185, Lahaina, Maui, HI. (808) 879-8182.

January 1-4—**Rheumatology and Immunology.** Symposium Maui, Inc. and Hawaii Medical Association, at Kaanapalo, Hawaii. Wednesday-Saturday. Contact: Joe Harrison, MD, Program Director Symposium Maui, Inc. PO Box 10185, Lahaina, Maui, HI 96761. (808) 879-8182 or 661-8032.

February 19-22—**10th Annual Course Immunology and the Clinical Practice of Allergy.** UCSD at Hilton Hotel, San Diego. Wednesday-Saturday. 20 hrs. Contact: Conference Management Associates, Edith S. Bookstein. (619) 454-3212.

March 19-23—**American Academy of Allergy and Immunology Annual Meeting** at San Francisco Hilton. Wednesday-Sunday. Contact: Executive Office, AAAI, 661 E. Wells St., Milwaukee, WI. (414) 272-6071.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

ANESTHESIOLOGY

January 9-12—**Anesthesia Update 1986.** UCSD at Hotel Del Coronado, San Diego. Thursday-Sunday. Contact: Kevie Naughton, Dept. of Anesthesiology, San Diego School of Medicine, (619) 452-3865.

January 24-26—**24th Clinical Conference in Pediatric Anesthesiology.** Pediatric and Anesthesiological Foundation and Childrens Hospital at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Wayne Herbert, Program Director, (213) 669-2262.

February 28-March 2—**Obstetric Anesthesia Update: State of the Art 1986.** UCSF at Hotel Meridien, San Francisco. Friday-Sunday. 13 hrs. Contact: Samuel C. Hughes, UCSF.

March 9-14—**Anesthesiology 1986.** Anesthesiology Education Foundation at Sierra Nevada Inn, Mammoth Lakes. Sunday-Friday. 20 hrs. Fee $250. Contact: UCLA.

May 5-9—**14th Annual Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Kauai, Monday-Friday. 20 hrs. Contact: Linda Londerville, (415) 348-1407.

June 19-22—**California Society of Anesthesiology Annual Scientific Meeting** at MGM Grand Hotel, Las Vegas. Thursday-Sunday. 17 hrs. Contact: Linda Londerville, 100 S. Ellsworth Ave., Suite 806, San Mateo, CA 94401.

CANCER

January 25—**Biomonitoring for Carcinogen Exposure in the Workplace.** UCI at UCI Social Science Tower, Irvine. Saturday. Fee: $100. Contact: R. E. Rasmussen, (714) 856-1064.

February 13-15—**The University of California Irvine First International Cancer Conference.** Memorial Medical Center of Long Beach at Newport Beach Marriott Hotel and Tennis Club, Newport Beach. Thursday-Saturday. 22 hrs. Contact: Center for Health Education, Long Beach, (213) 595-3811.

February 28-March 1—**Twenty First Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation at Sheraton Palace Hotel, San Francisco. Friday-Saturday. 12 hrs. Fee: $200. Contact: West Coast Cancer Foundation, San Francisco, (415) 981-4590.

March 6-8—**International Conference on Monoclonal Antibody Immunoconfates** UCSD at Hotel Intercontinental, San Diego. Thursday-Saturday. 19 hrs.

March 7—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Holiday Inn Union Square, San Fran-

(Continued on Page 734)

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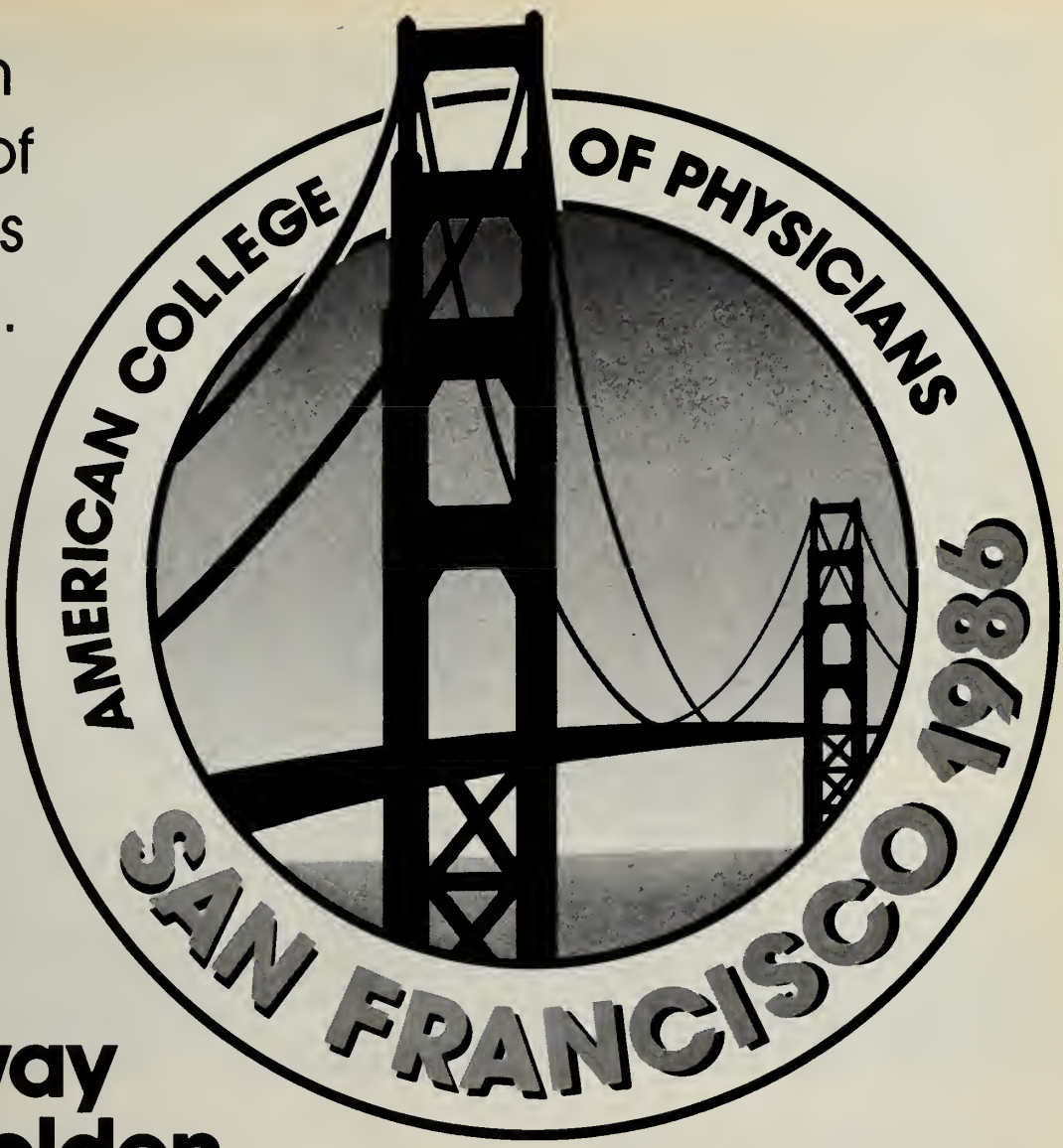

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834 **Overview of Marrow Transplantation**

E. DONNALL THOMAS, MD

From the Division of Oncology, Department of Medicine, the Fred Hutchinson Cancer Research Center and the University of Washington School of Medicine, Seattle.

838 **One Institution's Experience With Pancreas Transplantation**

DAVID E. R. SUTHERLAND, MD, PhD; FREDERICK C. GOETZ, MD; DAVID M. KENDALL, and JOHN S. NAJARIAN, MD

From the Departments of Surgery and Medicine, University of Minnesota Medical School, Minneapolis.

845 **Pancreas Transplantation—Registry Report and a Commentary**

DAVID E. R. SUTHERLAND, MD, PhD, and DAVID M. KENDALL

From the Department of Surgery, University of Minnesota Hospitals, Minneapolis.

853 **Pancreatic Islet Transplantation—Experimental Experience and Clinical Potential**

KEVIN J. LAFFERTY, PhD

From the Barbara Davis Center for Childhood Diabetes, Departments of Microbiology/Immunology and Pediatrics, University of Colorado School of Medicine, Denver.

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★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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cisco. Friday. 7 hrs. Fee: $145. Contact: J. Shiller, (619) 223-2997.

March 9—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sunday. 7 hrs. Fee: $145. Contact: J. Shiller, (619) 223-2997.

April 4—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Kona Kai Club, San Diego. Friday. 7 hrs. Fee: $145. Contact: J. Shiller, (619) 223-2997.

April 6—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. 7 hrs. Fee: $145. Contact: J. Shiller, (619) 223-2997.

CARDIOLOGY

January 30-February 1—**Cardiology 1986: Accomplishments and Expectations.** Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Thursday-Saturday. 13 hours. Fee $200-250. Contact: Nomi Feldman, San Diego, CA 92138. (619) 453-6222.

February 10-14—**First Annual Cardiovascular Conference at Hawaii.** Santa Barbara Heart and Lung Institute at Sheraton Waikola, Kona Hawaii. Monday-Friday. Contact: Registration Secretary Extramural Programs Dept. American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814.

February 12-13—**Reider Laser Center Symposium on Pulmonary Medicine.** Memorial Medical Center of Long Beach at Marquis Hotel, Palm Springs. Wednesday-Thursday. 8 hrs. Contact: Center for Health Education, Long Beach, (213) 595-3811.

February 14-16—**Pathophysiology and Techniques of Cardiopulmonary Bypass VI.** Cardiothoriacic Research and Education Foundation at The Sheraton Harbor Island East, San Diego. Friday-Sunday. 16 hrs. Fee: $275. Contact: Cardiothoriacic Research and Education Foundation, (619) 692-9115.

February 18-21—**Echocardiography Interpretation Workshop.** Straub Clinic and Hospital and the Institute for Medical Studies. Maui, Hawaii. Tuesday-Friday. 12 hrs. Fee: $325. Contact: Kim Stroich, (714) 495-4499.

February 21-23 —**Series II: Arrhythmias: Interpretation, Diagnosis, and Management.** Creighton University School of Medicine at Desert Inn Hotel Las Vegas. Friday-Sunday. 13 hrs. Contact: Leslie Shaffer, (303) 798-9682.

February 24-27—**4th Annual Cardiology Update.** Straub Clinic and Hospital and the Institute for Medical Studies at Honolulu, Hawaii. Monday-Thursday. 15 hrs. Fee: $395. Contact: Kim Stroich, (714) 495-4499.

February 24-28—**General Internal Medicine: Cardiology.** UCSF at Hyatt, Lake Tahoe, Monday-Friday. Fee: $365.

March 9-12—**Pulmonary Medicine.** UCSF Fresno at Ahwanhee Hotel and Yosemite Lodge, Yosemite National Park. Sunday-Wednesday. Contact: Sharon Balestra, Extended Programs in Medical Education, (209) 225-6100 ext. 562.

March 14-16—**The Clinical Approach to Excerise Testing Fitness Evaluation and Cardiac Rehabilitation.** IMEC at Hyatt at Union Square. Friday-Sunday. Fee: $360. Contact: Doris Price, Educational Programs Coordinator, IMEC, (800) 525-8651.

March 19-21—**Advances in the Management of Pulmonary Infections.** California Thoracic Society at Marriotts Santa Barbara. Wednesday-Friday. Fee: $300. Contact: Colleen McComas, (415) 638-5864.

March 21-23—**ECG Interpretation and Arrhythmia Management.** IMEC at Desert Inn, Las Vegas. Friday-Sunday. Fee: $360. Contact: Doris Price, (800) 525-8651.

March 24-26—**New Directions in Cardiac Rehabilitation.** Stanford. Monday-Wednesday. Contact: American College of Cardiology, 9111 Georgetown Rd., Bethesda, MD 20814

April 7-11—**Coronary Artery Disease: Hypertension Cholesterol and Risk Factor Management.** IMEC at Sheraton Waikiki. Monday-Friday. Contact: Doris Price, (800) 525-8651.

June 8-11—**Advanced Echocardiography and Doppler Ultrasound.** American College of Cardiology at Sheraton Harbor Island, San Diego. Sunday-Wednesday. Contact: American College of Cardiology, 9111 Georgetown Rd., Bethesda, MD 20814.

June 25-29—**Western Thoracic Surgical Association Annual Meeting.** WTSA at Silverado County Club, Napa. Wednesday-Sunday. Contact: TSA, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

June 26-28—**Conusltative Cardiology: Update in Diagnostic and Therapeutic Techniques.** ACC at The Westin South Coast Plaza, Costa Mesa. Thursday-Saturday. American College of Cardiology, (301) 897-5400.

June 30-July 2—**Cardiac Morphology: Clinical, Echocardiographic and Angiographic Correlations.** ACC at Hyatt Lake Tahoe Resort Hotel, Nevada. Monday-Wednesday. Contact: American College of Cardiology, (301) 897-5400.

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Clinical Clues to MIXED ANGINA

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The stairs seem steeper today

Most days she can climb the stairs with no difficulty. But today she was less than halfway up when an angina attack stopped her.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

And because vasoconstriction is an unpredictable event, ischemia and pain occur unpredictably

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- under emotional stress
- diurnally, typically in the morning

PROCARDIA® (nifedipine) is a primary therapy for the patient with MIXED ANGINA. It prevents vasoconstriction in both large coronary arteries and coronary arterioles to maintain myocardial blood flow and oxygen supply. At the same time, PROCARDIA dilates peripheral arteries to reduce afterload and myocardial oxygen demand.

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(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Reference

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use
INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers. **II. Chronic Stable Angina (Classical Effort-Associated Angina):** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete. Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.) **CONTRAINDICATIONS:** Known hypersensitivity reaction to PROCARDIA. **WARNINGS: Excessive Hypotension:** Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers. Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery. **Increased Angina:** Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone. **Beta Blocker Withdrawal:** Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA. **Congestive Heart Failure:** Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event. **PRECAUTIONS: General: Hypotension:** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.) **Peripheral edema:** Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction. **Laboratory tests:** Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has been demonstrated. Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some. **Drug interactions:** Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina. Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination. Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization. Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered. Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nitedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised. **Carcinogenesis, mutagenesis, Impairment of fertility:** Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative. **Pregnancy:** Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **ADVERSE REACTIONS:** The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, and erythromelalgia. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension. In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients. **HOW SUPPLIED:** Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Aspirin should not be taken during the last 3 months of pregnancy. ▫ **PRECAUTIONS**. Appropriate precautions should be taken in prescribing ZORprin® for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing ZORprin® for those patients with bleeding tendencies or those on anticoagulant drugs. Large doses of salicylates should be avoided in patients with clear evidence of carditis. 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Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid ZORprin®. Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal**: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from ZORprin® is designed to occur in the small intestine over a period of time. This has resulted in less symptomatic gastrointestinal side effects. **Allergic**: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. The most common allergic reaction to aspirin is the induction of bronchospasm with asthma-like symptoms. Other reactions are hives, rash, angioedema, as well as rhinitis and nasal polyps. 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CONTINUING MEDICAL EDUCATION

(Continued from Page 734)

EMERGENCY MEDICINE

December 9-13—**Postgraduate Institute for Emergency Physicians.** UCSD at La Jolla Village Inn, San Diego. Monday-Friday. 33 hrs. Fee: $215-$440.

January 13-17—**Postgradute Instructions for Emergency Physicians, Symposium I.** UCSD at Hanalie Hotel, San Diego. Monday-Friday. 33 hrs. Fee: $215-$440.

January 27-31—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Monday-Friday. Fee: $400.

February 23-28—**Emergency Medicine: 1986.** UCD at Hyatt Lake Tahoe. Sunday-Friday.

March 9-14—**Seventh Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sunday-Friday. 20 hrs. Fee: $325.

March 17-21—**Postgraduate Instutite for Emergency Physicians Symposium II.** UCSD at La Jolla Village, San Diego. Monday-Friday. 33 hrs. Fee: $440.

March 24-26—**Clinical Advances and Research Updates in Emergency Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Monday-Wednesday.

May 5-9—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD at Vacation Village Resort, San Diego. Monday-Friday. 33 hrs.

June 16-20—**Postgraduate Institute for Emergency Physicians: Symposium III.** UCSD at Hilton Beach and Tennis Resort, San Diego. Monday-Friday. 33 hr. Fee: $215-$440.

INTERNAL MEDICINE

January 18-25—**Infectious Disease and Toxicologic Emergencies.** Scripps Memorial Hospital at Kona Surf Resort. Kona. One week. 21 hrs. Fee: $350. Contact: Edith S. Bookstein, (619) 454-3212.

January 25-February 1—**1986 Infectious Diseases in Clinical Practice Audiotape Program.** UCSF at San Francisco General Hospital. One week. 33 hrs.

January 30-February 1—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Harbor Island West Hotel, San Diego. Thursday-Saturday. 18 hrs. Fee: $325.

January 31-February 1—**4th Annual Recent Advances in Infectious Disease.** UC Davis at Woodlake Inn, Sacramento. Friday-Saturday.

February 12-14—**Reider Laser Center Symposium on Urology.** UCI at Marquis Hotel, Palm Springs. Wednesday-Friday. 12 hrs.

February 14-19—**Hawaii Dermatology Seminar.** UCSF at Maui. Friday-Wednesday.

February 17-19—**Clinical Hematology and Oncology: 1986.** Scripps Clinic at Vacation Village Resort, San Diego. Monday-Wednesday. 19 hrs. Fee: $290. Contact: Dept. of Academic Affairs, (619) 457-8556.

March 20-22—**Gynecologic Urology: New Perspectives.** UCI at Palm Springs Hilton Hotel. Thursday-Saturday. 15 hrs.

March 25-26—**First International Symposium on the Clinical Update of the Female Reproductory Tract Infections.** Charles Drew Postgraduate Medical School at Disneyland Hotel, Anaheim. Tuesday-Wednesday. 8 hrs. Contact: Herbert Thomas, (213) 563-4927.

April 26—**Gastroenterology.** UCSF Fresno. Saturday.

OB/GYN

February 2-7—**OB/GYN: 1986.** UCD at Hyatt Lake Tahoe. Sunday-Friday.

February 12—**Progress in Gynecological Oncology.** Hospital of the Good Samaritan at Moseley Conference Center, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gray, (213) 977-2352.

February 12-14—**Reider Laser Center Symposium on Gynecology.** Memorial Medical Center of Long Beach at Marquis, Hotel Palm Springs. Wednesday-Friday. 12 hrs. Contact: Center for Health Education, (213) 595-3811.

February 21-23—**Office Gynecology for the Primary Care Physician.** UCSD at Hyatt Islandia, San Diego. Friday-Sunday. 18 hrs.

February 27-March 2—**Controversies in Obstetrics and Gynecology.** Memorial Medical Center of Long Beach at Royal Lahaina Resort, Hawaii. Thursday-Sunday. Contact: Margaret Frederick, (213) 595-3811.

February 6-9—**41st Annual Postgraduate Assembly: "New Assembly."** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thursday-Sunday. 28 hrs. Fee: $375. Contact: Director of Medical Education, (213) 937-5514.

April 11-13—**OB/GYN and Abdominal Sonography: Update 1986.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday.

OPHTHALMOLOGY

January 11—**Blepharoplasty: Cosmetic and Functional Surgery of the Eyelids.** UCLA at Jules Stein Eye Institute. Saturday.

January 17-18—**Advanced Vitrectomy Workshop.** UCLA at Jules Stein Eye Institute. Friday-Saturday.

January 30-February 1—**Lasers in Ophthalmology.** Stanford at Holiday Inn, Palo Alto. Thursday-Saturday. 18 hrs.

February 2-6—**Lake Tahoe Vitreoretinal Symposium.** UCD at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday.

February 28-March 1—**Fluorescein Angiography Techniques and Interpretation.** UCLA at Jules Stein Eye Institute. Friday-Saturday.

June 5-7—**Cosmetic Blepharoplasty Workshop.** UCLA at Jules Stein Eye Institute. Thursday-Saturday.

June 14—**Microsurgery and Laser Techniques for Glaucoma.** UCLA at Jules Stein Eye Institute. Saturday.

June 27-July 1—**Pacific Coast Oto-Opthalmological Society Annual Meeting.** UCLA at Hotel Intercontinental Maui. Friday-Tuesday.

PEDIATRICS

January 24-26—**24th Clinical Conference in Pediatric Anesthesiology.** Childrens Hospital Anesthesiology Foundation at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Wayne Herbert, (213) 669-2262.

February 26-March 5—**Third Annual Review and Update: General Pediatrics and Family Practice.** University of Nebraska Medical Center at Royal Waikiloa Hotel, Kona. One week. 20 hrs. Contact: University of Nebraska Medical Center, (402) 559-4152.

March 5-12—**Third Annual Review and Update: General Pediatrics and Family Practice.** University of Nebraska Medical Center at Royal Lahaina Hotel, Maui. One week. 20 hrs. Contact: University of Nebraska Medical Center, (402) 559-4152.

March 6-9—**Medical and Legal Perspectives in Perinatal Medicine: The Ninth Annual San Diego Symposium.** San Diego Reproductive Medicine Research and Education Foundation at Hotel Inter-Continental, San Diego. Thursday-Sunday. 16 hrs. Contact: Reproductive Medicine Research and Education, (619) 692-9115.

March 29-April 5—**Pediatric Emergencies.** Scripps Memorial Hospital at Waiohai and Poopy Beach. Kauai. One week. 21 hrs.

May 22-23—**3rd Annual Current Issues in Anatomic Pathology.** UCSF at Union Square Holiday Inn, San Francisco. Thursday-Friday.

(Continued on Page 870)

The Benefits of Less

Low doses of hydrochlorothiazide can provide most of the antihypertensive effect of larger doses.[1]

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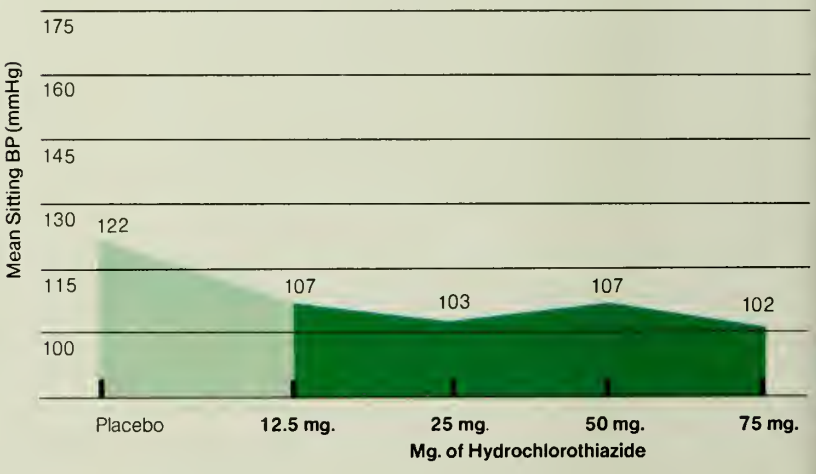

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1 Kaplan, N Systemic Hypertension: Therapy, in Braunwald, E. (ed.), Heart Disease A Textbook of Cardiovascular Medicine, Philadelphia, W.B Saunders Co., vol. 1, pp. 922-951.

2 Dialogues in Hypertension, Hypertension Update II· New Developments in Antihypertensive Therapy, Jan 1985, Health Learning Systems Inc.

3. Adapted from Beerman, B., and Groschinsky-Grind, M.: Antihypertensive Effect of Various Dos of Hydrochlorothiazide and Its Relation to the Plasma Level of the Drug, Eur. J. Clin. Pharmacol. 13: 195-201, 1978.

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

★ **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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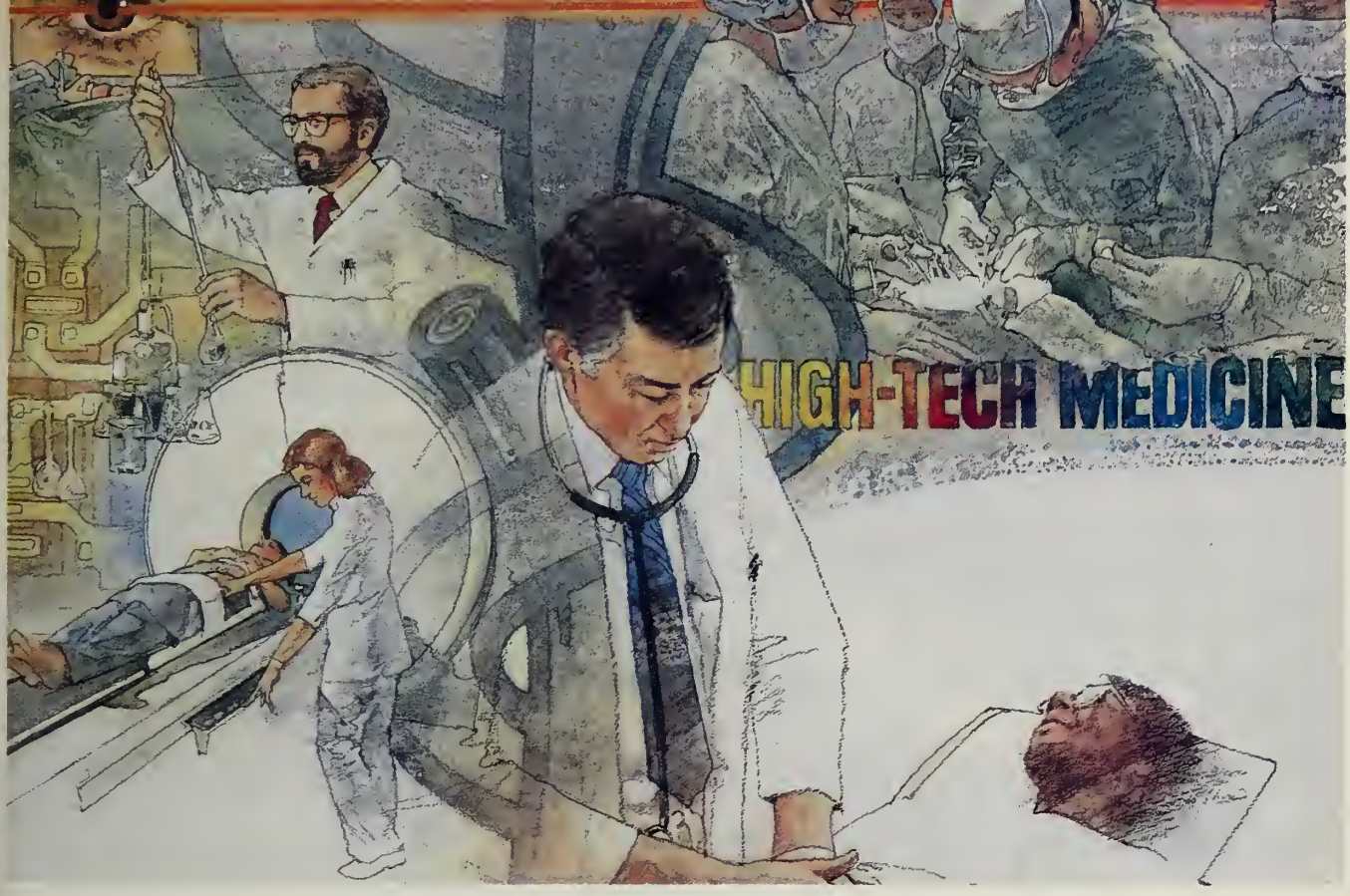

High-Tech Medicine

Each year *The Western Journal of Medicine* presents a special issue in December on a topic important for physicians. In recent years the subjects have been personal health care maintenance (1984), cross-cultural medicine (1983), occupational/environmental medicine (1982), geriatrics (1981), cost of care (1980) and clinical nutrition (1979).

This year the editors selected "High-Tech Medicine" to be the topic for the December 1985 Special Issue. Today's high-tech medicine reflects the cutting edge of progress in medical science. It is just the beginning of what is certain to be an unprecedented payoff on the enormous investment that has been and is being made in the research that is pushing back the frontiers of medical and health science. The future holds untold benefits for the betterment of mankind. The articles in this issue address some, but certainly not all, of these frontiers of experiment and progress that are opening new vistas of effective patient care, where within the memory of many of us, there was little or nothing that could be done.

No attempt has been made here to address all the ethical, social, economic or political problems that high-tech medicine raises. These are profound, indeed, and they are being discussed as appropriate in this and other journals. This issue will have fulfilled its purpose if it gives its readers a glimpse of some of the progress toward what is certain to be only the beginnings of what high-tech medicine holds for the future of health care, and for human society as a whole.

The editors are most grateful to R. Paul Robertson, MD (who has been our special editor for the clinical investigation series in the journal), for his work in preparing this special issue and for stimulating and assembling the fascinating papers that appear herein. We thank him for his work on this issue, and for his significant contributions to the development of the section on clinical investigation, and we wish him well in his new assignment at the University of Minnesota, where he will be after July 1, 1986.

MSMW

Star Wars in Medicine—Good and Bad Fallout

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

This *WJM* special issue was orchestrated to bring you up to date on some of these more current, impressive advances. We are very indebted to the authors—all authorities in their fields—for accomplishing the difficult task of making complex science comprehensible to nonexperts. The good fallout from these impressive scientific advances for present and future medical practice will become readily apparent as you absorb the contents of each article. Enjoy.

But a note of caution. Even with such good fallout from medical progress, there can be bad fallout. I recall my physician father grumbling in the early 1950s about unrealistic pressures from his patients to use antibiotics in inappropriate clinical circumstances following the spectacular success of sulfa and penicillin. In the 1980s, his son is concerned about pressures our scientific community might place on investigators to immediately incorporate new scientific techniques into their research. Valuable as they are, these techniques will be poorly served if we rush lemminglike to clone antibodies or buy expensive imagers simply to be avant-garde. We will all do well to thoughtfully use only techniques that are truly appropriate to our research. And as grant proposal reviewers, we will do a real service by continuing to support tried and true techniques that continue to provide us with valuable insights into medical disease.

R. PAUL ROBERTSON, MD
Special Issue Editor
Editor for Clinical Investigation

Lasers in Ophthalmology

GEORGE A. MOO-YOUNG, MD, PhD, *Denver*

An increased understanding of laser-tissue interactions in ophthalmology has led to the use of lasers in treating a wide spectrum of diseases involving both the anterior and posterior segments of the eye. These diseases include the four commonest causes of blindness in the United States: diabetic retinopathy, age-related macular degeneration, glaucoma and cataract. As knowledge of the operating characteristics and treatment limitations of lasers increases, the use of lasers in the treatment of other ophthalmologic problems will be broadened.

(Moo-Young GA: Lasers in opthalmology, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:745-750)

The history of science in general, and medicine in particular, is replete with those serendipitous moments when an important new discovery precipitates a flood of solutions to old problems and, assuming a life of its own, generates a host of applications to other problems as well. One of these moments in ophthalmology occurred in 1960, when T.H. Maiman discovered the ruby laser.[1]

Although this laser was used on a limited basis because of technical factors (instability of the beam and inconvenient pulse duration), subsequent generations of new lasers, such as the argon, krypton and neodymium (Nd):YAG (yttrium-aluminum-garnet) lasers, have made it possible to treat effectively the four commonest causes of blindness in the United States: diabetic retinopathy, age-related macular degeneration, glaucoma and cataract. Other lasers, such as the carbon dioxide, tunable dye and excimer lasers, currently enjoy fewer applications but are being used experimentally in certain select cases.

The purpose of this paper is to review briefly the characteristics of these lasers and to illustrate their more common uses in ophthalmology.

Laser Characteristics

Coherence

The special feature of lasers that makes them so effective is that of coherence, both spatial and temporal. Spatial coherence allows precise focusing of the laser beam to widths as small as a few microns, while temporal coherence allows selection of monochromatic wavelengths within a single laser or a family of lasers. The practical implication of spatial coherence, therefore, is that extremely small burns to pathologic tissue can be made, with minimal disturbance to surrounding normal tissue. Temporal coherence, on the other hand, allows treatment of specific tissue sites by selecting laser wavelengths that are preferentially absorbed by these tissue sites.

Laser-Tissue Interaction

Laser-tissue interactions can occur in several ways, depending on the power, pulse-duration and wavelength indices chosen. They are broadly grouped under photothermal, photochemical and photoionizing effects.

Photothermal effects. Photothermal effects include photocoagulation and photovaporization-photocarbonization. In the first instance, absorption of light by the target tissue results in a temperature rise, which causes denaturization of proteins. Typically, argon and krypton lasers, with wavelengths in the visible spectrum, are used in photocoagulation and cautery. Photovaporization occurs when higher energy laser light is absorbed by the target tissue, resulting in vaporization of both intracellular and extracellular water. When the local store of water is vaporized, photocarbonization occurs. The advantage of this type of tissue response is that adjacent blood vessels are also treated, resulting in a bloodless surgical field. The carbon dioxide laser, with its wavelength in the far infrared, uses this method of action and is used primarily for bloodless incisions.

Photochemical effects. Photochemical effects include photoradiation and photoablation. In the former, intravenous administration of hematoporphyrin derivative, which is taken up by the target tissue, causes sensitization of the target tissue. Exposure of this sensitized tissue to red laser light induces the formation of cytotoxic free radicals. Tunable dye lasers are used for this purpose. Photoablation occurs when high-energy laser wavelengths in the far ultraviolet (<350 nm) region of the spectrum are used to break long-chain tissue polymers into smaller volatile fragments. In contrast to the photoradiation effect, where relatively long exposure times

Dr Moo-Young is Clinical Instructor, Department of Ophthalmology, University of Colorado Health Sciences Center, Denver, and in private practice in Denver. Reprint requests to George A. Moo-Young, MD, PhD, 950 East Harvard Ave, Suite 300, Denver, CO 80210.

TABLE 1.—*Ophthalmologic Lasers*

Laser	*Wavelength, nm*	*Tissue Effect*	*Ophthalmologic Uses*
Excimer	193 (far UV)	Photochemical	Photoablation (incision)
Argon	488 (blue) 514.5 (green)	Photothermal	Photocoagulation (coagulation)
Krypton	530.9 (green) 568.2 (yellow) 647.1 (red)	Photothermal	Photocoagulation (coagulation)
Dye	Variable	Photochemical	Photoradiation (cytotoxic)
Neodymium:YAG	1,064 (near IR)	Photoionization	Photodisruption (incision)
Carbon dioxide	10,600 (far IR)	Photothermal	Photovaporization/ photocarbonization (incision)

IR = infrared, UV = ultraviolet, YAG = yttrium-aluminum-garnet

(minutes) are necessary to produce the cytotoxic free radicals, the exposure times in the photoablation process must be much shorter (nanoseconds) compared with diffusion times necessary for heat conduction into surrounding tissue (milliseconds). Excimer lasers, using this mechanism of action, are being used experimentally to produce precise cuts in corneas[2] and to disrupt intravitreal membranes.[3]

Photoionization effects. Photoionization occurs when high-energy light is deposited over a short interval to target tissue, stripping electrons from the molecules of that tissue. This cloud of electrons and ionized molecules constitutes a "plasma," which then rapidly expands, causing an acoustic shock wave that disrupts the treated tissue. The ND:YAG laser uses this "photodisruptive" mechanism in lysing secondary cataract membranes and vitreous membranes.

The operative wavelength of these lasers is shown in Table 1. Although we have tried to categorize laser-tissue interactions into three main groups, it must be kept in mind that for each laser system, there may be some overlap in the laser-tissue interactions noted above. Judicious selection of wavelength, power and pulse-duration, as well as an understanding of the tissue absorption characteristics, will optimize the clinical use for which the laser is intended. These are the goals of current laser research, especially for the newer generation of lasers, such as the Nd:YAG and excimer lasers.

Clinical Uses of Lasers—Anterior Segment

Glaucoma

Glaucoma is a rise in the intraocular pressure of the eye that occurs when the aqueous humor formed by the vitreous body fails to gain access to or is impeded at the outflow channel of the eye, the trabecular meshwork. In a normal eye, the aqueous is formed by the ciliary body in the posterior chamber, passes between the posterior iris surface and the anterior capsule of the lens, gains access to the pupillary space and travels to the trabecular meshwork, through which it is filtered, and subsequently leaves the eye via blood-aqueous channels (Figure 1).

The angle formed by the iris and the cornea, the apex of which is the trabecular meshwork, normally is about 20 to 45 degrees. In eyes with a propensity for narrow-angle glaucoma to develop, the angle may be quite narrow—about 10 to 20 degrees (Figure 2). In an acute episode of narrow-angle glaucoma, the anterior surface of the lens occludes the pupil. Aqueous flow diminishes through this pupillary block, and increased posterior chamber pressure balloons the peripheral iris root forward, creating an iris bombé and resulting in closure of the angle, with a subsequent acute rise in the intraocular pressure (Figure 3). In conventional glaucoma management, a surgical iridectomy is done to allow the aqueous trapped behind the iris to flow into the anterior chamber, to

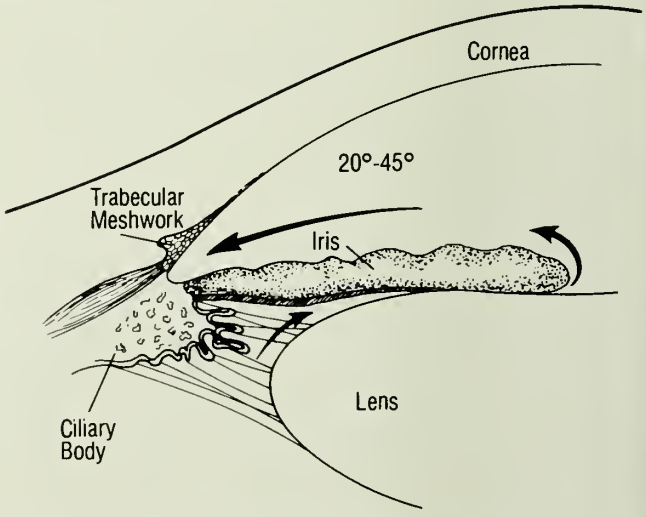

Figure 1.—Anatomy of the normal angle and the anterior segment of the eye. Arrows show the direction of flow of the aqueous.

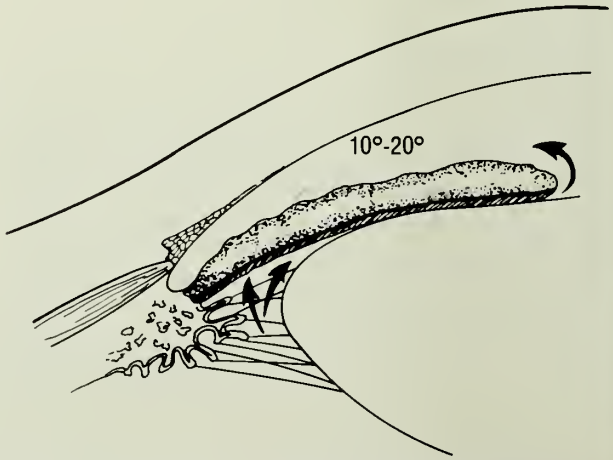

Figure 2.—Narrow angle with iris root bowed forward slightly.

widen the angle and to permit aqueous to escape through the trabecular meshwork. With laser surgery, however, argon, krypton or Nd:YAG lasers may be used to create an iridotomy (hole in the iris), thus relieving the pupillary block (Figure 4). The advantage of this technique is that the procedure is noninvasive and requires neither admission to hospital nor regional anesthesia. Cataract formation, a complication of surgical iridectomy, can be avoided. The disadvantages of laser iridotomy are few, but include an inadvertent retinal burn through a patent iridotomy. If this burn occurs on the peripheral retina, the damage is minimal. Should it occur in the macula, however, the central vision may be decreased. Because the iridotomy occurs in the peripheral iris, away from the optical axis, macular burns are extremely rare. In addition, repeated attempts at laser iridotomy may be needed in blue or edematous irides.

Open-Angle Glaucoma

In primary open-angle glaucoma, there is obstruction to aqueous outflow, probably at the level of the trabecular meshwork. When medical management fails, argon or krypton laser trabeculoplasty can be done. In this procedure, 50-micron spot-sized burns are made at the level of the trabecular meshwork. The intensity of the burns is selected to create scars that contract and pull the meshwork open.[4] Although this is the most common hypothesis to explain the mechanism of action of the trabeculoplasty, the exact mechanism is unknown.[5] The advantages of laser trabeculoplasty are many. The procedure obviates the need for hospital admission, regional anesthesia and an intraocular surgical procedure with all its attendant complications such as flat chamber, cataract, choroidal hemorrhage and infection. The procedure, however, works in some eyes only, and, in those that initially respond favorably, a repeat intraocular pressure rise may occur a few months to years later.

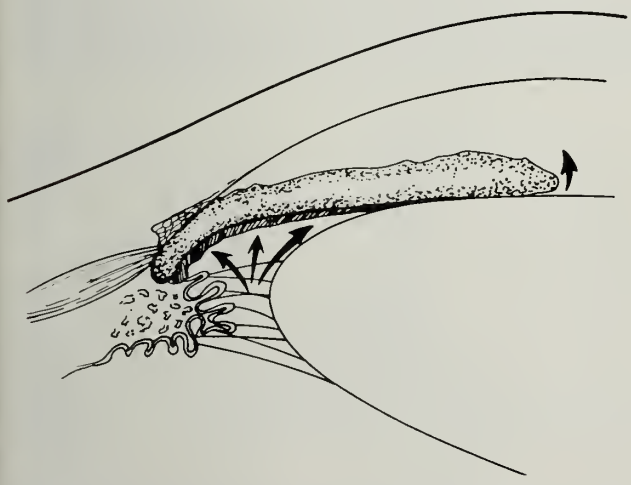

Figure 3.—The angle has closed and the peripheral iris root has occluded the trabecular meshwork, blocking the egress of aqueous from the anterior chamber.

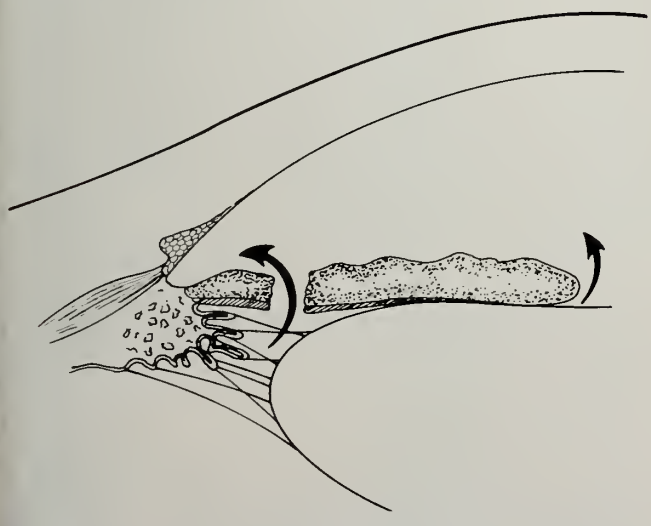

Figure 4.—A peripheral iridotomy has allowed aqueous trapped behind the iris to gain access to the anterior chamber angle and the trabecular meshwork.

In secondary open-angle glaucoma, as seen in patients with diabetic retinopathy and central retinal vein occlusion, it is thought that the hypoxic retina elaborates an angiogenic factor, which stimulates the formation of neovascular tissues in the retina and, later, in the angle. This angle neovascularization subsequently leads to fibrosis, closure of the angle and glaucoma. Most of the time, panretinal photocoagulation, using the argon or krypton laser, will lead to regression of these angle blood vessels. However, concomitant argon or krypton angle (gonio-) photocoagulation may be necessary to cauterize residual angle blood vessels in those cases where the neovascular stimulus remains.

Aphakic Malignant (Ciliovitreal Block) Glaucoma

In some patients with aphakia, the anterior hyaloid surface of the vitreous can occlude the pupillary opening, diverting aqueous into the posterior chamber. In this type of glaucoma, the angle is generally shallow, despite the presence of a surgical iridectomy. The aqueous cannot gain access to the anterior chamber, resulting in a rise in intraocular pressure. Nd:YAG hyaloidotomy can be done to create a channel for the posteriorly directed aqueous to reach the anterior chamber.[6] Such an outpatient procedure would be the treatment of choice for this disorder and would preclude surgical vitrectomy and its attendant complications.

Laser Capsulotomy

One technique of cataract extraction is a "planned extracapsular extraction" with or without placement of an intraocular lens within the eye. In this technique, the anterior capsule of the lens is surgically removed, along with the nucleus and cortex of the lens, leaving intact the posterior capsule of the lens. Of the patients who have undergone the procedure, a significant proportion will have opacification of the posterior capsule, with resulting loss of vision. The usual surgical procedure for correcting this condition is to incise the capsule with a thin knife or to remove the capsule with a vitrectomy cutter. However, as an outpatient procedure, noninvasive capsulotomy can be done with the Nd:YAG laser, immediately restoring vision. This is accomplished by photodisruption of the capsule by an expanding shock-wave of the plasma, which is generated by the laser. With inaccurate positioning of the laser light, damage to the cornea, iris, intraocular lens and retina may occur but is extremely rare.

Clinical Uses of Lasers—Posterior Segment

Early clinical use of the argon laser in the posterior segment was devoted largely to the treatment of diabetic retinop-

athy. While this trend has continued, use of the argon laser has expanded to include treatment of other retinal and choroidal neovascular diseases, of which diabetic retinopathy and age-related macular degeneration are the respective prototypical diseases. Other current uses of the laser in the posterior segment include treatment of retinal tears, with or without small localized retinal detachment, and some tumors of the posterior segment.

Current investigative work is under way on the use of the Nd:YAG and excimer lasers in lysing vitreoretinal bands.

Retinal Neovascular Disease

Diabetic retinopathy, branch vein occlusion, central vein occlusion and sickle cell retinopathy are the most common retinal neovascular diseases encountered by an ophthalmologist. The underlying pathophysiologic mechanism common to these entities is a vaso-occlusive phenomenon occurring on the venous side of the circulation in diabetic retinopathy and the vein occlusions and on the anterior side of the circulation in sickle cell retinopathy. In each instance, nonperfusion of the retina leads to tissue hypoxia. It is believed that, as a consequence of this, the hypoxic retina liberates an angiogenesis factor, which stimulates the formation of neovascular tissue, usually at the junction of perfused and nonperfused retina. The treatment of this neovascular proliferation is to destroy the hypoxic retina so that most of the stimulus for neovascularization is reduced or eliminated. This type of laser treatment is called panretinal photocoagulation. Diabetic retinopathy and the vein occlusions affect not only the peripheral retina but also the retina bounded by the superior and inferior temporal veins—the "posterior" pole—the center of which is the macula. Macular edema is a common feature of these venous occlusive diseases. In some cases, argon or krypton laser photocoagulation may be effective in alleviating the degree of macular edema, with the use of focal treatment to the leaking area. In contrast, sickle cell retinopathy primarily affects the far retinal periphery, and so peripheral panretinal photocoagulation is the treatment of choice in those eyes at risk for vitreous hemorrhages.

Diabetic retinopathy. Diabetic retinopathy is primarily a disease of the retinal capillaries. The earliest pathologic changes in these capillaries are loss of the tight junctions of the endothelial cells and formation of microaneurysms within the vessel walls. Leakage of serum, erythrocytes or both into the retinal interstitium takes place. If this occurs near the posterior pole, macular edema results, with concomitantly reduced visual acuity. These early changes are part of the complex called background or nonproliferative diabetic retinopathy. The pattern of macular edema may fall into one of three categories: focal (circinate), diffuse or cystoid. In the first instance, the source of leakage is located and, after cauterization or photocoagulation, the edema resolves and visual acuity is improved (Figure 5). The efficacy of argon or krypton laser photocoagulation in treating diffuse or cystoid macular edema, however, is less defined but is currently being investigated within the Early Treatment Diabetic Retinopathy Study being conducted by the National Eye Institute.

In the later stages of nonproliferative diabetic retinopathy, endothelial proliferation leads to closure of the capillary lumens, resulting in capillary nonperfusion and hypoxia of areas of the retina usually served by these capillaries. It is felt that these hypoxic areas of the retina initiate the release of an angiogenic factor, which stimulates the formation of neovascular tissue, usually at the junction of perfused and nonperfused retina on the optic nerve head and, in certain cases, on the surface of the iris (rubeosis iridis) and the trabecular meshwork. These developments are part of the complex called proliferative diabetic retinopathy. If left untreated, retinal neovascular tissue will grow on the adjacent vitreous cortex. As the cortex retracts or exerts traction on these abnormal blood vessels, vitreous hemorrhages of varying severity will occur. Similarly, untreated neovascularization of the trabecular meshwork in the anterior chamber of the eye can lead to neovascular glaucoma.

Argon or krypton laser panretinal photocoagulation of these areas of hypoxic retina, it is believed, decreases the stimulus for formation of these neovascular areas, and therefore aims at stabilization or regression (or both) of these blood vessels (Figure 6). The ultimate goal of panretinal photocoagulation is not primarily to improve vision but to prevent the occurrence of vitreous hemorrhages by causing involution of the proliferative retinopathy. The results of the Diabetic Retinopathy Study conducted by the National Eye Institute in the 1970s show that panretinal photocoagulation in patients with proliferative diabetic retinopathy and certain high-risk factors reduces the risk of severe visual loss by 50% or more.[7,8]

Patients undergoing panretinal photocoagulation usually receive 1,500 to 3,000 laser burns of 500-micron diameter in the peripheral retina over two or three treatment sessions. The number of burns necessary to achieve involution of the proliferative retinopathy will vary from patient to patient. Indeed, because of renewed vasoproliferation, some patients may require additional laser burns months or years after the initial treatment. Although most patients experience only mild to moderate pain, some may require a retrobulbar anesthesia for more severe pain. Complications are few and are primarily related to the ablation of the peripheral retina—that is, constriction of the peripheral field and a decrease in night vision due to destruction of the photoreceptors in the peripheral retina. In most patients, however, these symptoms may preexist because of the vascular compromise of the peripheral retina; consequently, no new symptoms are noted after laser photocoagulation. Corneal and lenticular burns are reported but are rare complications of the laser treatment. In some eyes, choroidal effusions and secondary angle glaucoma will develop following treatment, but these conditions are infrequent and generally self-limiting. Occasionally, increased macular edema of varying duration will also occur in susceptible patients after treatment.

Branch and central vein occlusions. In branch vein occlusions, retinal hypoxia occurs in the distribution of the occluded vein and may elicit a neovascular response in the affected area. Sector panretinal photocoagulation is then the treatment of choice. In addition, macular edema may develop and may be successfully treated with focal laser photocoagulation, resulting in vision improvement.

In central vein occlusions, generalized retinal hypoxia may lead to neovascularization of the optic nerve, peripheral retina and anterior segment, necessitating panretinal photocoagulation and supplemental goniophotocoagulation. Here, the purpose of the treatment is not to improve vision but to prevent the development of recurrent vitreous hemorrhages

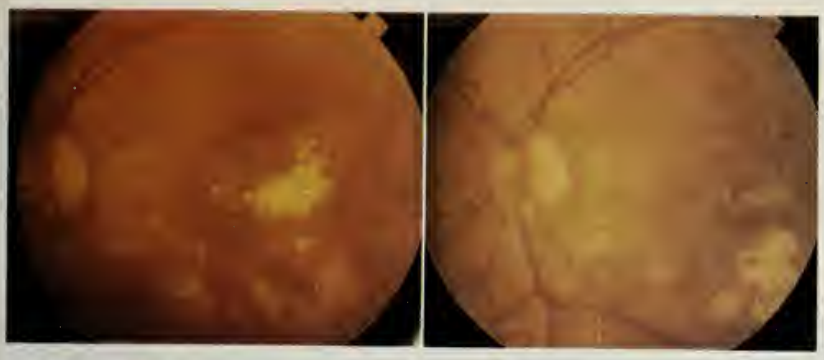

Figure 5.—Left, The fundus of the left eye before laser photocoagulation in a patient with lipid leakage into the macula. Site of the leakage is along the inferior temporal border of the macula. Visual acuity is 20/200. **Right,** The fundus of the same eye after photocoagulation, showing absorption of the lipid material. Laser scars are seen at the original site of the leakage. Visual acuity is 20/70. Secondary pigmentation from the previously present lipid material is seen in the macula.

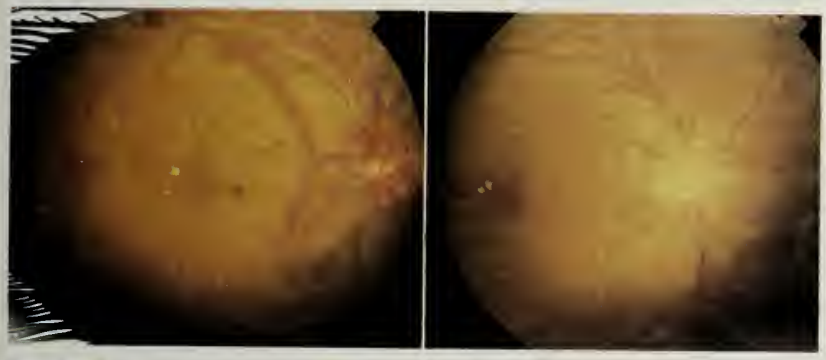

Figure 6.—Left, The fundus of the right eye before laser photocoagulation in a patient with proliferative diabetic retinopathy showing exuberant neovascularization of the optic nerve head. **Right,** The same eye after laser panretinal photocoagulation and showing almost total regression of the vascular component of the neovascular tissue.

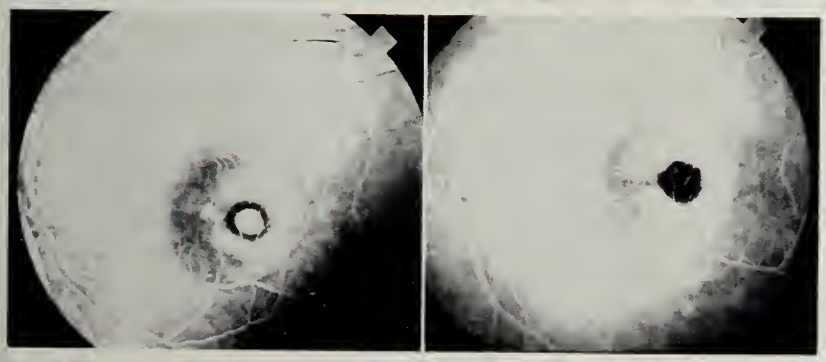

Figure 7.—Left, Fluorescein angiogram showing the left eye of a patient with age-related macular degeneration. The circular area of hyperfluorescence temporal to the macula represents leakage from choroidal neovascular membrane (50-degree field). **Right,** Postlaser photocoagulation angiogram of the treated neovascular membrane, showing obliteration of the neovascular tissue (30-degree field).

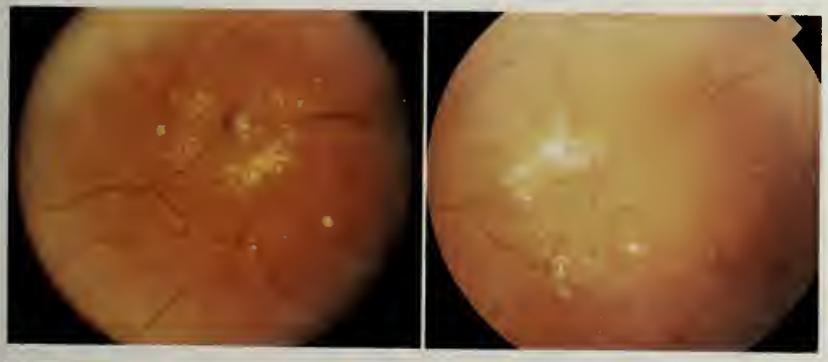

Figure 8.—Left, The fundus of the left eye before laser photocoagulation in a patient with Coats' disease. Note the leakage of lipid from a telangiectatic area of the blood vessel (circinate pattern). Other areas of telangiectasis without associated leakage are seen below the circinate pattern (30-degree field). **Right,** The fundus of the same eye postlaser photocoagulation showing sclerosis of the telangiectatic area and resolution of the leakage. Note that the treated blood vessel is still patent distal to the treated area. Although the inferior areas of telangiectasis have enlarged since the laser treatment, there continues to be no lipid leakage from these areas (50-degree field).

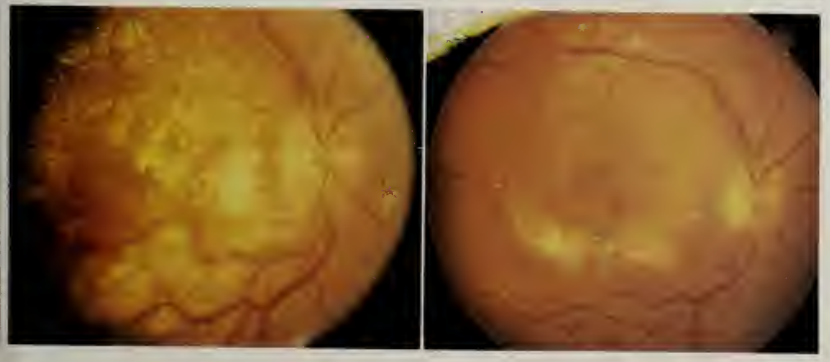

Figure 9.—Left, The fundus of the right eye before laser photocoagulation in a patient with a retinal macroaneurysm. Note the extensive circinate retinopathy surrounding the macroaneurysm. Visual acuity is counting fingers at 6 ft (30-degree field). **Right,** Postlaser photocoagulation fundus of the same eye. Note total resolution of the lipid leakage and continued patency of the treated blood vessel. Visual acuity is 20/60 (50-degree field).

and neovascular glaucoma. The prognosis for the return of good vision is poor, even with subsequent spontaneous recanalization of the central vein.

Sickle cell retinopathy. In sickle cell retinopathy, peripheral arteriolar occlusion leads to secondary proliferative retinopathy. Sector peripheral panretinal photocoagulation will induce involution of these blood vessels. Sickle cell and sickle-thalassemia traits are the sickle cell diseases generally associated with retinopathy.

Choroidal Neovascular Diseases

Choroidal neovascular diseases, of which age-related macular degeneration is the most common, can sometimes be successfully treated with focal argon or krypton laser photocoagulation. Other treatable diseases within this category include the ocular histoplasmosis syndrome, idiopathic choroidal neovascularization and choroidal neovascularization due to angioid streaks and traumatic breaks in Bruch's membrane. The common pathophysiology associated with these diseases is a break in Bruch's membrane, which is sandwiched between the retina and the choroid. This membrane normally acts as a barrier to vascular migration from the choroid to the subretinal space. When Bruch's membrane is breached, however, blood vessels from the choroid can gain access to the subretinal space. If these areas of neovascularization involve the center of the macula (fovea) or are within the avascular zone surrounding the fovea, laser photocoagulation will not improve the vision since treatment of the subretinal neovascular tissue will necessitate foveal or parafoveal damage. In age-related macular degeneration, for instance, only 5% of the patients with this condition can be treated. For the remaining 95% of patients, the location of neovascular tissue precludes focal treatment. In eligible patients, visual distortion and decreased vision will resolve after successful focal laser photocoagulation (Figure 7).

Abnormal Blood Vessels

Coats' disease and retinal arteriolar macroaneurysms are two conditions in which direct focal treatment of these vessels will result in improved vision. In Coats' disease, telangiectasis of the retinal vessels is present. These areas tend to leak serum in the retinal interstitium, and if this occurs near the macula, macular edema and decreased vision will result (Figure 8). Reversal of this process occurs when the abnormal blood vessels are successfully treated.

Interstitial retinal edema is generally more pronounced in patients who have leaking retinal arteriolar macroaneurysms, but it is also treatable when direct photocoagulation is applied to these vessels. The purpose of the treatment is not to occlude the arteriole, since this might result in retinal apoplexy distal to the macroaneurysm, but rather to scarify the arteriolar walls, resulting in decreased leakage (Figure 9). Patients with arteriolar macroaneurysms may have an associated systemic hypertension.

Retinal Tears

Retinal tears with or without small localized retinal detachments can be treated with focal laser photocoagulation. This method of treatment involves placing several confluent laser burns in attached retina around the perimeter of the retinal tear in an attempt to spot-weld the retina in place. If an associated small localized retinal detachment is present, the laser burns are placed in attached retina around the perimeter of the detachment.

Intraocular Tumors

Selected cases of malignant melanoma, retinoblastoma and retinal angiomas can be treated with focal argon or krypton laser photocoagulation. Other traditional modalities of treatment for these tumors are available, including cryocoagulation and irradiation with external beam, cobalt plaque or particle beam (proton or helium ion). Photoradiation of melanomas, presensitized by hematoporphyrin derivative and treated with red tunable dye lasers, has also been investigated. Further work will determine the position that focal argon or krypton laser photocoagulation will occupy in the hierarchy of treatments available for these tumors.

Summary

The use of lasers in ophthalmology has permanently altered the traditional ways of treating certain eye disorders. Invasive surgical intervention for some glaucomas and cataracts has been replaced by outpatient laser procedures. The visual prognosis for patients with diabetes mellitus has improved significantly with laser photocoagulation, and patients with treatable choroidal neovascular diseases have responded well to laser surgical techniques. Treatment of other retinal neovascular and abnormal vascular diseases with laser photocoagulation enjoys a high success rate. As continuing clinical research further defines the operating characteristics and indications for the use of existing and newer generations of lasers, ophthalmologists will be able to treat a broader spectrum of eye diseases with greater precision and safety.

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Endoscopic Gastrointestinal Laser Therapy

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The development of flexible fibers for the delivery of laser energy led to the first endoscopic laser applications in humans in the early 1970s. Since that time, much has been learned about applications throughout the gastrointestinal tract. The risks appear to be minimal. The coagulative effect of laser energy is used to treat gastrointestinal hemorrhage and small, benign mucosal lesions. The ablative effect of the Nd:YAG laser on tissue is used for palliative therapy for malignant gastrointestinal disorders and incisional therapy for anatomic lesions such as strictures or cysts. New laser modalities that potentially can be tuned throughout large segments of the electromagnetic spectrum, new fiber-optic delivery systems with specialized tips and new methods of sensitizing tissue to laser energy all indicate that the endoscopic laser should continue to have many new and innovative applications.

(Buchi KN: Endoscopic gastrointestinal laser therapy, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec;143:751-757)

The phenomenon of *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation occurs when an atom or molecule is excited to a higher energy state and then is stimulated to emit a photon of light energy by returning to its resting state; the device used to exploit this phenomenon is the *laser*. Each atom or molecule emits electromagnetic energy of a specific wavelength. The emissions of the photons can be amplified in the laser medium between two mirrors. One mirror is fully reflective, the other only partially so; this allows the photons of energy to be directed from the laser chamber. The laser energy exiting the medium is in the form of an intense beam of monochromatic (single wavelength) light. It is also coherent light—that is, all the photons of energy are in phase.[1]

When coherent laser energy, or the laser beam, interacts with tissue, it is absorbed or scattered; the effect depends on a number of variables. These include the thermal conductivity of the tissue; the amount of blood circulating in the tissue, which carries heat away; the power and duration of the laser pulse, and the wavelength of the laser energy. Each wavelength has a differential absorption and thus has a relatively predictable depth of tissue penetration.

As laser energy is absorbed it is converted to heat, and increasing tissue temperatures lead progressively to cell death, protein coagulation, blood vessel constriction and water and tissue vaporization. These effects are visible endoscopically and determine the outcome of the laser-tissue interaction.

As seen in Table 1, the delayed outcome of laser energy delivered to tissue can be divided into two major categories: below 100°C (212°F), coagulation of the targeted tissue occurs, followed by slough and repair; at or above 100°C, vaporization or ablation of the tissue occurs. The coagulative effect is useful in treating acute gastrointestinal hemorrhage, arteriovenous malformations and small, benign mucosal lesions. The ablative effect is used to destroy neoplastic tissue or to cut through tissue to treat anatomic lesions such as strictures or cysts. Each of these five major applications will be reviewed.

Laser Applications

Acute Gastrointestinal Hemorrhage

The development of fiber-optic delivery systems for laser energy in the early 1970s made endoscopic applications possible. At about the same time, Dwyer and Frühmorgen and their colleagues used the argon laser to control gastrointestinal bleeding in humans.[2,3] Feeling that more power was needed, Kiefhaber and associates experimented with and were the first to report clinical use of the neodymium (Nd)-yttrium-aluminum-garnet (YAG) laser.[4]

Although these initial successes established that laser therapy could be delivered endoscopically, they raised two important questions. First, could endoscopic laser treatment control gastrointestinal bleeding effectively and with an acceptable complication rate? Second, when compared with current standards of medical and surgical care, would laser therapy be the treatment of choice for acute gastrointestinal bleeding?

Numerous uncontrolled trials have answered the first ques-

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TABLE 1.—*Thermal Effects of Laser-Tissue Interaction*

Tissue Temperature, °C	Physiologic Event	Endoscopic Tissue Appearance	Delayed Outcome
45	Cell death, edema, vasodilation	Erythema, edema	Cell death, inflammation
60 to 80	Coagulated proteins, contraction of collagen and blood vessels	Tissue turns gray, white, or brown; blood turns black	Death, slough and ulceration, followed by repair
100	Tissue water vaporizes	Hole or ulcer in tissue	Tissue ablated
210	Dehydrated tissue burns	Black tissue glows and disappears; sparks may form	Tissue ablated

tion affirmatively. The largest single series is that of Kiefhaber and associates,[5] who reported achieving initial hemostasis in 94% of 994 acute bleeding episodes involving 625 patients over a seven-year period. Recent reviews of these trials indicate that the argon laser successfully achieved initial hemostasis in 70% to 80% of more than 300 patients, with a subsequent rebleeding rate of 10% to 15%. The Nd-YAG laser achieved initial hemostasis in 80% to 90% of more than 2,000 patients reported, with a rebleeding rate of about 10% in cases of ulcer, but a 30% rebleeding rate for esophageal variceal hemorrhage.[6,7] Perforation rates for both lasers were low, ranging from 1% to 3%.

These uncontrolled studies also made major contributions to the technical aspects of laser endoscopy. Refinements in laser equipment, the importance of using a coaxial carbon dioxide flow to aid visualization and to keep the fiber tip clean and the addition of such safety aspects as gas recirculation to avoid overdistention of hollow organs were all outgrowths of these trials. Concurrently, there was extensive analysis of the depth of gastrointestinal tissue penetration with both argon and Nd-YAG lasers, using varying power densities and durations of application. Excellent summaries of the results of these investigations have recently been published.[8,9]

Although these reports proved that an endoscopically delivered laser energy could effect hemostasis, the question remains whether lasers are the treatment of choice. The incidence of recurrent hemorrhage, the length and cost of hospital stay and morbidity and mortality associated with the laser treatments all had to be considered in comparison with the results of standard medical and surgical therapy for gastrointestinal hemorrhage. Controlled, randomized trials were necessary to establish the value of laser therapy for acute gastrointestinal hemorrhage.

Nine controlled studies of laser treatment for patients with acute upper gastrointestinal bleeding have now been reported.[10–18] Although more than 700 patients have been included in these trials, only about half of those patients were actively bleeding when randomly selected.

The use of the argon laser was studied in three trials.[10–12] Direct comparisons among these are somewhat difficult because of differences in the patient groups, the inclusion and exclusion criteria and the endpoints of treatment. The results, as summarized in Table 2-A, are mixed. Swain and coworkers showed that laser treatment produced a significant decrease in the rebleeding rate and in the survival rate for patients with a visible vessel.[10] Vallon and colleagues did not show an overall difference between the laser-treated and the control groups; laser treatment, however, was beneficial in those patients with active bleeding from a visible vessel and in whom the laser could reach the lesion.[11] Jensen and associates showed a definite benefit to their patients from laser treatment, but their groups are small.[12]

The results of six randomized, controlled trials on the use of the Nd-YAG laser in acute gastrointestinal bleeding have been published. Five of these included patients who had only or primarily peptic ulcer disease. Comparisons among these, too, are hampered by variability in the patient selection criteria and by various stratifications of the patients into those with active bleeding and those with stigmata of recent hemorrhage (visible vessel, adherent clot).

In Table 2-B these five studies are summarized after selecting out only those patients in whom active bleeding was

TABLE 2.—*Controlled Trials of Lasers for Gastrointestinal Bleeding**

Investigators	Series Patients C	Series Patients L	Initial Hemostasis C	Initial Hemostasis L	Hemostasis >1 Wk C	Hemostasis >1 Wk L	Emergent Surgery C	Emergent Surgery L	Death C	Death L
	Number		Number		Number		Number		Number	
A. Argon Laser										
Swain et al, 1981[10]	9	10	0	10	5	6	2	4	2	0
Vallon et al, 1981[11]	13	15	4	10	2	8	9	7	3	2
Jensen et al, 1982[12]	6	6	2	6	NS	NS	4	0	1	0
B. Nd-YAG Laser										
Ihre et al, 1981[13]	19	15	NS	14	4	7	5	6	5	4
Escourrou 1981[14]	30	31	14	21	10	5	6	7	2	2
Rutgeerts et al, 1982[15]	40	46	31	46	25	43	5	1	6	6
Swain et al, 1983[16]	41	41	NS	NS	23	38	14	3	5	1
MacLeod et al, 1983[17]	8	8	0	8	0	6	8	1	2	0
Fleischer 1985[18]	10	10	0	7	3	3	NS	NS	7	4

C = control, L = laser treated, Nd-YAG = neodymium yttrium-aluminum-garnet, NS = not studied or not reported

*Results have been abstracted where possible to include only actively bleeding patients.

seen at the time of random selection or treatment. The studies by Ihre and Escourrou and their colleagues failed to show any significant differences in long-term hemostasis, the need for surgical treatment or survival, although initial hemostasis was achieved in a large number of the laser-treated patients.[13,14] The trial conducted by Ihre and associates, however, included many patients with esophageal variceal hemorrhage.

Rutgeerts and colleagues showed a significant decrease in the rebleeding rate and the need for an urgent operation in the laser-treated patients, but the mortality of the treated patients did not differ from that of the controls.

The studies by Swain and MacLeod and their co-workers were particularly well done.[16,17] They precisely defined the bleeding point and included only patients with ulcer disease. The patients were stratified into specific groups: those with active bleeding, those with visible vessels and those with other stigmata of recent hemorrhage. The results of these studies show a definite benefit in hemostasis and survival in the laser-treated groups when compared with the controls.

The sixth randomized study, done by Fleischer, was exclusively concerned with patients bleeding from esophageal varices.[18] Although initial hemostasis was achieved in 70% of the patients in this group, rebleeding was common and no overall benefit of laser treatment could be seen. These results are in agreement with the poor results for treating variceal hemorrhage seen in the study by Ihre and associates and the earlier reports of uncontrolled series.

Complication rates were not systematically addressed in these studies, but they appear to be in the same range as in the earlier uncontrolled studies. No perforations were reported, and a 5% to 10% incidence of increased hemorrhage after laser treatment was seen.

Several points can be learned from these trials. First, laser therapy for active gastrointestinal hemorrhage appears to be beneficial only in patients with actively bleeding peptic ulcer disease or with nonbleeding visible vessels in an ulcer crater. Second, certain lesions are not suited to laser therapy: esophageal varices, diffuse gastritis and lesions inaccessible to the laser beam. Third, these studies have helped to define the importance of the so-called visible vessel, or the sentinel clot,[19] in identifying patients at high risk of rebleeding. Certainly, more patients need to be evaluated, but this knowledge may help to eventually reduce the morbidity and mortality from gastrointestinal hemorrhage. Fourth, the complications specifically related to laser use are few when trained endoscopists do the laser therapy.

In light of these findings, the laser is now used at the University of Utah as one of several tools for dealing with acute gastrointestinal bleeding. In patients with actively bleeding vessels in an ulcer crater, or nonbleeding visible vessels, either the Nd-YAG laser or contact thermal coagulation, or both, is used, depending on which modality can best reach the lesion or control the bleeding. Neither is routinely considered to be definitive therapy. Rather, they are temporizing measures to achieve hemostasis and allow resuscitation, after which decisions for elective surgical therapy or continued medical therapy with close observation can be made based on other patient characteristics. The laser is not used for variceal hemorrhage because endoscopic sclerotherapy is more effective in that situation.

Vascular Malformations

As fiber-optic endoscopy has become routine in the evaluation of gastrointestinal bleeding, the importance of mucosal vascular lesions as a cause of acute and chronic hemorrhage has been recognized.[20] These lesions range in size from less than 1 mm to 2 cm or more. Some are hereditary, as in Osler-Weber-Rendu disease, and can be responsible for blood loss beginning at a young age. Others are acquired, occasionally in association with aortic valvular disease, portal hypertension or renal disease, and occur in older patients. Attempts have been made to classify the lesions on the basis of histologic criteria,[20] but widespread agreement has not been reached. As a result, the lesions are known by a variety of terms, including angiodysplasia, arteriovenous malformation, telangiectasia and others. Regardless of the terminology, these vascular malformations are particularly amenable to laser therapy. They tend to be mucosal, rarely more than 1 to 2 mm deep and, because they are vascular, they absorb light energy well in the argon-laser wavelength.

Reports from several centers have described the clinical use of endoscopic laser energy to treat these lesions.[21-25] Three centers have used the argon laser. Waitman and coworkers treated 50 patients, stopping the bleeding in 33 of them and substantially decreasing transfusion requirements in 17.[21] No complications occurred, despite an average patient age of 73 years. Jensen and colleagues reported a similar benefit in a group of 17 patients with vascular malformations and 8 patients with Osler-Weber-Rendu disease; again, there were no complications.[22] Hunter and co-workers at the Laser Institute at the University of Utah have reported results on 40 patients with vascular malformations that were located throughout the gastrointestinal tract, including 4 patients with the Osler-Weber-Rendu disease[23]; most of these patients were treated with the argon laser. A few required the higher power of the Nd-YAG laser. The bleeding was stopped or considerably reduced in 36 of these 40 patients, with a follow-up period of 1 to 40 months. There were no complications related to the laser endoscopy. Since the last report, another 21 patients with vascular malformations and 5 patients with Osler-Weber-Rendu disease have been treated. The results in these patients are similar to the earlier ones, and there continue to be no complications.

Two groups of researchers have used the Nd-YAG laser for treating vascular malformations, with similar results. Etienne and colleagues reported controlling bleeding in three patients who had Osler-Weber-Rendu disease,[24] and Fleischer reported controlling bleeding in five patients with gastric and duodenal vascular malformations, with a one- to eight-month follow-up period.[25]

The collective experience of these centers has established that laser treatment of gastrointestinal vascular malformations is safe and that it effectively stops bleeding or decreases it considerably. The safety record is particularly impressive in light of the preponderance of elderly patients in each series. The argon and the Nd-YAG lasers appear to be equally effective, although the argon laser is adequate for most lesions and would be expected to produce fewer complications, such as perforation, over the long term. All investigators have reported an occasional increase in bleeding when treatment is started, but in all cases the bleeding has been successfully controlled with continued laser applications.

Benign Mucosal Lesions

The uniform, shallow penetration of tissue by the argon laser suggested that it might be appropriate for the ablation of benign gastrointestinal mucosal lesions. Dixon and coworkers reported the results of studies in animals and humans verifying that colonic mucosa and mucosal lesions could be ablated with minimal risk of penetration or perforation.[26] After its safety was established, the laser was applied in 11 patients with Gardner's syndrome. These patients had had prior subtotal colectomy with ileorectal anastomosis, which necessitated periodic rigid sigmoidoscopy for fulgurating recurrent polyps. After appropriate biopsies, 211 polyps were photocoagulated in 18 treatment sessions in the 11 patients. Follow-up endoscopy showed necrosis and sloughing of the treated tissue at four days, which left small mucosal ulcerations that had healed completely by 12 days in all cases. These patients then had periodic surveillance sigmoidoscopy, with argon phototherapy for new polyps as they were discovered. More than 500 polyps have subsequently been treated without complications in these patients.[23] Two patients have required proctectomy for progressive mucosal dysplasia, and an additional three patients have had elective ileoanal pull-through operations.

The argon laser has also been used to ablate sporadic sessile adenomatous colon polyps in patients in whom surgical treatment or electrocautery could not be safely done.[23] Other successfully treated lesions include gastric polyps,[27] endometriosis of the colon[23] and residual islands of columnar mucosa in a patient who had undergone esophagectomy with colonic interposition for Barrett's esophagus.[23]

These reports have established that the argon laser can be safely used for benign mucosal lesions in the gastrointestinal tract. Enthusiasm must be tempered, however, by the fact that many of these disorders have dysplastic potential and that a histologic diagnosis cannot be confirmed when the laser is used to ablate lesions. As experience accumulates, such lesions may be treated primarily with laser ablation, but currently this cannot be recommended.

Malignant Gastrointestinal Lesions

Palliative therapy for malignant gastrointestinal tumors is one of the more appealing applications of endoscopic laser surgical treatment. All areas that can be reached with a fiberoptic endoscope can potentially be treated for neoplasms and most have been, including the esophagus, stomach, duodenum, ampulla of Vater, biliary tract, colon and rectum.

Many malignant tumors occurring in hollow organs do not become symptomatic until they are large enough to cause bleeding or obstruction. By that time, most are incurable by surgical resection, yet this is often necessary for palliation. Radiation therapy plays a role in these patients as well, but is often associated with undesirable systemic side effects and is limited by potential damage to the surrounding normal tissue.[28]

The management of obstructing or bleeding tumors with endoscopic laser treatment would not be expected to improve survival in these patients when compared with surgical or radiation therapy, but it does have several important advantages:

- It can be done with minor sedation, thus avoiding the risks of general anesthesia and a major surgical procedure.
- It can be done in many cases on an outpatient basis, thereby reducing medical costs and avoiding prolonged hospital stays.
- It can be applied on a recurrent schedule because there is no limiting cumulative dose for laser energy.
- Although there are definite risks involved, systemic side effects are few, thus increasing patient acceptance of the therapy.

The major indications for laser therapy for gastrointestinal tumors are obstruction and bleeding. Laser therapy for debulking a tumor mass when obstruction or bleeding is not present is appealing, but offers no proven benefit, nor does treatment solely for pain relief.

In the United States the earliest application of laser therapy for malignant gastrointestinal disorders was that of Fleischer and associates, who reported the successful relief of dysphagia in five patients with obstructing squamous cell carcinoma of the esophagus.[29] Their experience now includes 40 patients who were not considered candidates for surgical or radiation therapy.[30] Most of these patients had dysphagia with 90% or more occlusion of the esophageal lumen. Of the 40 patients, 37 improved symptomatically, with endoscopically determined luminal diameters increasing from a mean of 2.8 mm to 11.5 mm. Clinical improvement typically lasted for three to six months, and some patients were then successfully treated again. Tracheoesophageal fistulas or perforations developed in five patients (12%); two of those were clearly laser related, but the other three occurred as late as six months after laser treatment and may have been related to the underlying tumor.

Mellow and Pinkas reported similar results in 11 patients and also noted a median survival time of 36 weeks, compared with a 17-week survival for matched historical controls.[31] They suggest that the improved survival time was due to the patients' ability to maintain better nutrition after laser canalization. This is an attractive explanation, but it needs verification.

Several research groups have reported using the Nd-YAG laser for palliative and, in some selected instances, curative therapy for gastric cancers. Fleischer and Sivak reported the successful relief of obstruction in 15 patients with adenocarcinomas at the gastroesophageal junction.[32] Although this area is difficult to work in because the esophagus often makes an angle as it enters the stomach, no laser-related perforations occurred. The complications, including pain, low-grade fevers and transient leukocytosis, were mild.

Other investigators have reported similar results, although with smaller numbers of patients.[23,33,34] The experience at the University of Utah Laser Institute now totals 14 patients—all of whom had their obstructions relieved. Ten patients had inoperable or recurrent squamous cell carcinomas, and four had adenocarcinoma obstructing the gastroesophageal junction (Figure 1). Two tracheoesophageal fistulas have developed in this group, one clearly related to the laser treatment. Mean survival has been four to six months, but one patient received periodic treatments and was able to eat until he died of metastatic disease 13 months later (Figure 2).

Promising reports from Japan have suggested that early, broad-based gastric cancers or premalignant "borderline" lesions may be cured by ablation with the Nd-YAG laser.[35]

Unfortunately, such lesions are rarely found in Western populations, where widespread screening is not cost effective.

There have been other reports of the argon laser providing relief from gastric outlet obstruction caused by recurrent gastric carcinoma,[36] and that choledochoscopic Nd-YAG laser therapy controlled hemobilia and malignant biliary obstruction.[37] Further applications in the upper gastrointestinal tract can be expected as experience with the laser continues to expand.

Experience is also being gained in the use of ablative laser therapy in the colon. The major indications for the use of laser therapy in colorectal neoplasms remain the relief or preven-

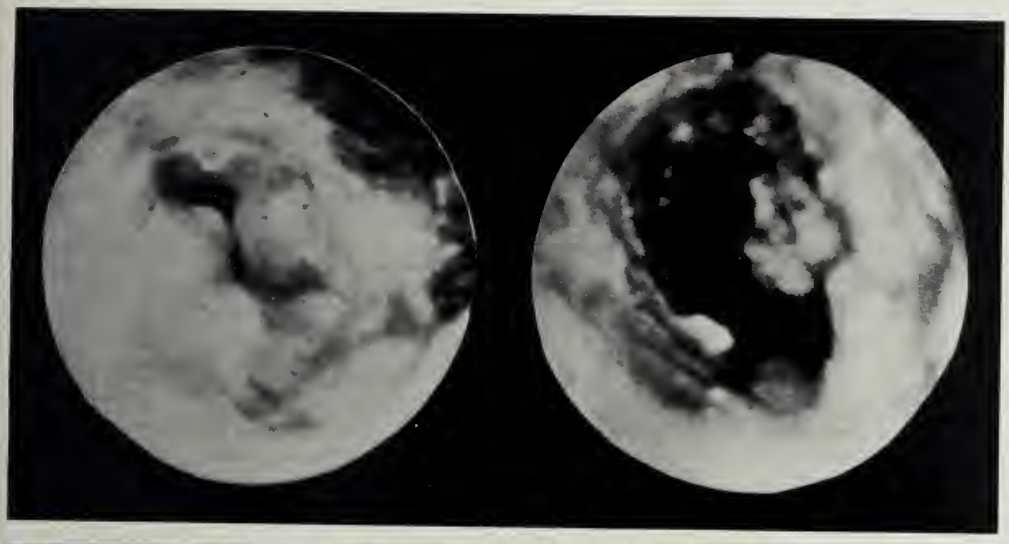

Figure 1. Left, Endoscopic view of an adenocarcinoma obstructing the gastroesophageal junction. **Right,** Its appearance following laser recanalization.

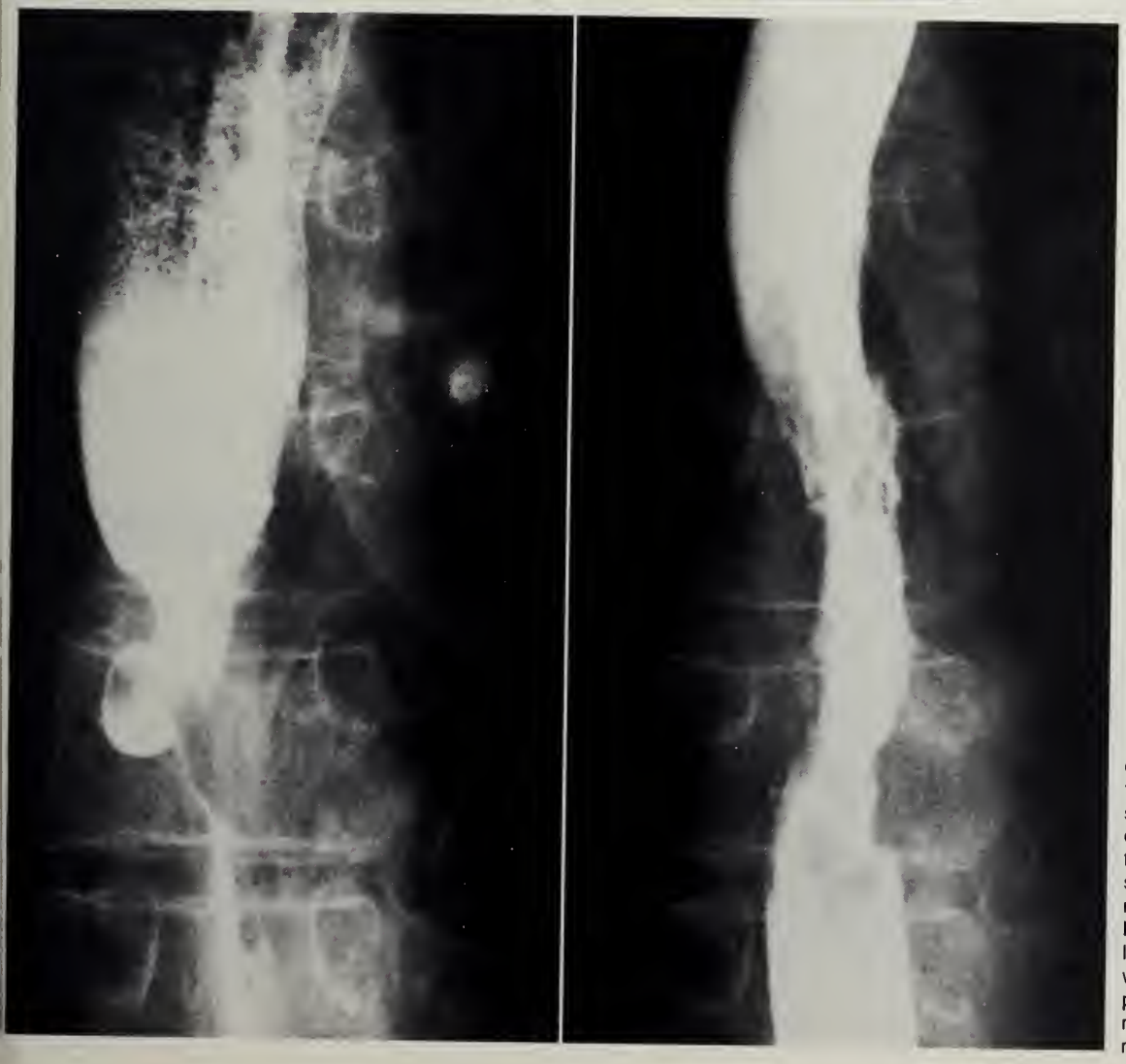

Figure 2. Left, Barium swallow showing an obstructing mid-esophageal squamous cell carcinoma. The tumor had not responded to a full course of radiation therapy. **Right,** The same patient one month later, following laser recanalization. Patency was maintained with periodic laser treatments for 13 more months.

tion of obstruction and the control of bleeding. A third major use of laser therapy in the colon is to photoablate large premalignant adenomas that are not amenable to electrosurgical resection or that occur in patients who are not candidates for surgical treatment (Figure 3). Brunetaud and Mosquet have reported on their treatment of 25 cases of rectal cancer with the Nd-YAG laser.[38] Functional improvement or control of bleeding was achieved in one to two weeks by treating patients an average of twice a week. Luminal patency was then maintained with treatments about once a month. No major complications were reported.

Hunter and co-workers reported the successful relief of obstruction or the control of hemorrhage in seven patients with rectal cancer.[23] Five of the patients were still alive at the time of the report, without recurrence of bleeding or obstruction, after a mean of 7.6 months of follow-up, and two died of metastatic tumor or coronary disease. No perforations occurred, and the only complication was one episode of transient bleeding during vaporization of the tumor. Both the argon and Nd-YAG lasers were used initially, but the increased power and depth of penetration of the Nd-YAG laser ablated the tumor much quicker. The Nd-YAG laser is now used almost exclusively at the University of Utah for this work.

Two centers in Europe have reported extensive experience with Nd-YAG laser therapy for inoperable premalignant colorectal lesions. Lambert and Sabben reported complete photodestruction of 35 out of 39 villous adenomas and a reduction in the size of the lesion in the remainder.[39] Four perforations were noted, but two of the patients were asymptomatic and no deaths occurred. Brunetaud and Mosquet reported curing 27 of 37 patients who had this problem, with a reduction in the size of the adenomas in all but two of the remainder. The average follow-up for these patients was 8.3 months.

In summary, laser photoablation therapy offers effective palliation for specific groups of patients with a malignant gastrointestinal tumor. Relief from obstruction allows a patient with esophageal or gastric cancer to continue to eat or a patient with colorectal cancer to continue to defecate. Skilled endoscopists can provide relief to patients with either disorder with a low incidence of complications, thereby avoiding the physical trauma of a major operation or the emotional trauma of feeding tubes or ostomy appliances.

Patients who have small colorectal cancers or premalignant lesions may also benefit from laser therapy, but caution must be used. Currently, appropriate candidates for laser treatment should be patients whose disorder is inoperable because of coexisting diseases, or in whom standard electrosurgical resection cannot be used because of the size, configuration or location of the lesion. Close follow-up surveillance must be maintained.

The development of newer methods of treatment, such as intralesional laser fibers,[40] will expand the ability to safely treat tumors endoscopically. The use of tissue-sensitizing agents in clinical work is also improving our technique.[41] These agents alow for more precise photoradiation therapy to be applied to tumor tissue with less risk of damage to the surrounding normal tissue. Such advances offer future promise; it is likely that laser applications in various forms will continue to expand in the palliative and, perhaps eventually, the curative treatment of malignant gastrointestinal conditions.

Incisional Laser Applications

The ability of lasers to vaporize and ablate tissue can also be used for incisional therapy for nonmalignant gastrointestinal lesions. Potential applications are limited only by the ability to reach the desired area endoscopically, and this broad applicability is reflected in the diversity of lesions that have already been treated. Delmotte and co-workers used the argon laser to drain chronic pancreatic and biliary cysts internally.[42] Buchi and colleagues used the Nd-YAG laser to drain two symptomatic and expanding immature traumatic pancreatic pseudocysts.[43] An area of gastric wall overlying the pseudocysts was photocoagulated, then allowed to slough away and create a large pseudocystogastrostomy. The cysts drained, were obliterated and did not recur during a three-year follow-up period.

Several reports have described the successful use of the laser for incisional enlargement of postoperative intestinal stenosis,[23,44,45] peptic strictures[46] and various congenital rings and webs.[23,47] The Nd-YAG laser has been used to

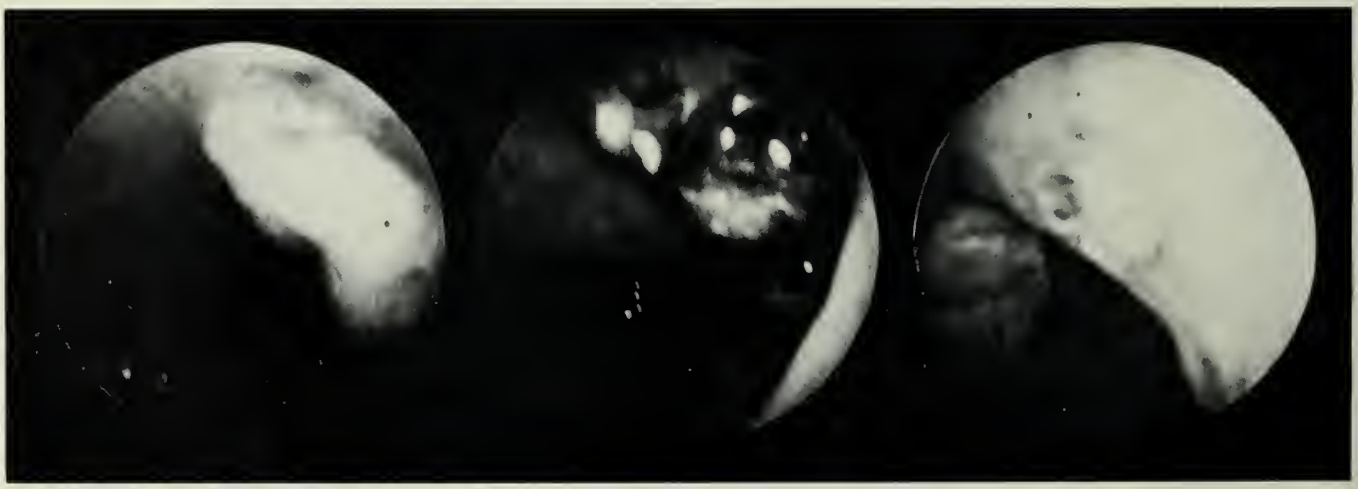

Figure 3.—A 3-cm rectal villous adenoma seen before (**left**), immediately after (**center**) and two weeks following (**right**) neodymium-yttrium-aluminum-garnet laser photocoagulation. The ulcer remaining after the treated adenoma sloughed away healed completely by four weeks after treatment.

fragment biliary stones after percutaneous access was permitted by a choledochoscope.[48] Such innovative incisional applications are in an early investigational phase, but promise to greatly influence the practice of gastrointestinal surgical treatment.

Future Considerations

A remarkable body of experience has been accumulated in the use of lasers in gastroenterology. Lasers have been used to stop gastrointestinal bleeding, palliate the effects of malignant gastrointestinal tumors and deal with a number of anatomic problems. Endoscopic laser surgical treatment must still be considered to be in its infancy, however, especially when it is remembered that the first applications in humans occurred only within the past decade.[2,3]

Only lasers of two wavelengths have had appreciable use: the argon and the Nd-YAG. Tunable-wavelength and free-electron lasers are being developed; these will allow a large segment of the electromagnetic spectrum to be used. These other wavelengths will likely have specific tissue effects and applications that we cannot yet foresee. The availability of a fiber-optic delivery system for the carbon dioxide laser holds the possibility of many new incisional and resective endoscopic applications. Contact probes for improved hemostasis with less energy and snare-tipped or knife-tipped laser fibers are also in investigational stages and will likely expand the utility of the laser as an endoscopic tool. Continued progress in evaluating tissue-sensitizing agents should allow for the more precise destruction of malignant tissue with less damage to the surrounding normal tissue.

Finally, it must be remembered that endoscopic equipment continues to be refined, opening new areas of the gastrointestinal tract to access for the delivery of laser energy. In short, the outlook for laser endoscopy is bright, and the field of its application should continue to expand as the technology improves.

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Cutaneous Laser Therapy

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The carbon dioxide laser is useful for vaporizing lesions and applying incisions, the argon laser coagulates superficial vascular lesions and the neodymium-YAG laser is used for large vascular and more deeply situated lesions. Many patients with port-wine stains have been treated with excellent to poor results, major problems consisting of incomplete color removal and hypertrophic scarring (occurring in 4% to 23% of cases). While results are imperfect, patients are satisfied with the improvement in 86% of cases. Lasers have been used with good results for treating patients with strawberry angioma of infancy, pyogenic granuloma, telangiectasia of the face, decorative tattoos, genital condylomata and warts. The results of laser treatment of essential telangiectasia of the lower extremities have generally been poor. The CO_2 laser has been effective in excising small lesions and elevating skin flaps.

(Dixon JA, Gilbertson JJ: Cutaneous laser therapy, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:758-763)

This year the Smithsonian Institution is preparing an exhibit commemorating the 25th anniversary of the invention of the laser by Maiman.[1] It is interesting that laser application to the skin was one of the first suggested medical uses of this new and powerful instrument. The stated reasons for such early interest are the unique optical properties of the skin and the unusual absorption, transmission and scattering noted. More likely explanations are that this long-suffering organ was readily available, laser-tissue interactions could be seen easily and, after all, the skin was used to having light of various wavelengths applied to it.

Among the early investigators, Leon Goldman deserves special mention.[2] This intrepid pioneer bypassed the usual governmental regulations by making various laser applications to his own skin, followed by involved, continuous and dedicated observation of the results. Following this, he extended his practice to include patients and induced a number of other investigators and clinicians to become active in this field. Today, cutaneous applications are among the most common uses of the laser in medicine.

In this article we provide a brief overview of cutaneous laser therapy and describe laser-skin interaction as well as some major clinical applications to vascular and nonvascular lesions.

The limitations of this presentation do not allow for a discussion of the considerable research in the field, details in technique or a number of unique but less frequent clinical applications. Appropriate references are provided for readers interested in more specific information.

Laser Instruments and Tissue Response

The lasers in most common clinical use are the argon (488 to 515 nm), carbon dioxide (10.6 microns) and neodymium-yttrium-aluminum-garnet (YAG) (1.06 micron) instruments. Each has certain unique characteristics. There is a great deal of overlap, however, when the primarily thermal effects of the lasers are being used. For instance, a skilled operator can remove a decorative tattoo by coagulating or vaporizing with any of the three wavelengths with approximately the same results.[3]

There are, however, certain differences in laser-tissue interaction that are important. The argon laser is probably the most commonly used for skin therapy. Argon laser energy is about 98% absorbed in 1 mm of blood and only about 2% absorbed in 1 mm of water. The nonhomogeneous but highly vascular character of the skin results in penetration and coagulation to a depth of about 1 mm with selective injury absorption by hemoglobin in the vessels of the epidermis and dermis.[4]

Instruments are relatively small, portable and inexpensive. Laser energy may be conducted from a power source by a small quartz fiber-optic device to which lenses may be attached to control the size of treatment spots.

There is an appreciable but lesser degree of absorption of the argon energy by melanocytes and dermal collagen. This

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absorption plus diffusion of heat absorbed by hemoglobin and vessels results in considerable nonspecific skin damage during laser therapy. At higher powers (10 to 15 W), vaporization occurs that is similar to that noted with the carbon dioxide laser.[5]

The CO_2 laser wavelength is heavily absorbed by water; thus, cells are readily vaporized due to the intense heat generated. Where the argon laser leaves a coagulum about 1 mm in depth per application, the CO_2 laser leaves a crater 0.1 mm in depth, with a surrounding area of thermal necrosis of 50 to 100 microns.[6] These characteristics make this laser useful in lesions requiring incision, vaporization or precise removal.

The CO_2 laser, pictured in Figure 1, is very useful for skin applications. Current technology does not allow CO_2 energy transmission via fiber optics. Hence, rather bulky articulating arms consisting of a series of reflecting mirrors must be used. This frequently precludes precise application in inaccessible areas but does not interfere with the treatment of most flat surfaces.

Figure 1.—The carbon dioxide laser is suitable for dermatologic and plastic procedures on skin, having a 30 W output, with a flexible articulating arm (Cooper LaserSonics, Inc).

The neodymium-YAG laser is very large, relatively immobile and expensive. Typical units generate powers of as high as 100 W.

This laser is less often used on the skin but is frequently helpful with large, nodular, vascular lesions as the laser penetrates to a depth of 3 to 4 mm and produces intense coagulation. The neodymium-YAG laser energy is much less absorbed by blood and can penetrate more deeply in vascular tissue.[7]

The ruby laser is bulky, not portable and relatively difficult to use. It is infrequently used at a few centers throughout the world for removing melanotic lesions.[8]

Vascular

Port-Wine Stains

Port-wine stains have been known since antiquity as the "red birthmark." This lesion occurs in about 0.3% of the population and is especially distressing when it occurs on the face. Port-wine stains appear at birth, do not tend to become larger but do become darker colored and more nodular with age.[9] Spontaneous resolution does not occur as it does with strawberry angiomata.

The lesion may be associated with a number of syndromes such as Klippel-Trenaunay (port-wine stain with limb hypertrophy), Sturge-Weber (port-wine stain plus intracranial calcifications and meningeal involvement), Kissebach-Merritt (port-wine stain plus consumption coagulopathy) or glaucoma.

Patient selection for treatment is very important. Children younger than age 12 years tend to scar more, especially around the upper lip (Figure 2).[10] Lesions of the trunk and extremities tend to scar more than those of the face and neck. Darker, red-purple lesions tend to show more improvement than light pink ones.

Figure 2.—Hypertrophic scarring of the lip **(arrow)** is seen in a 13-year-old boy following argon laser therapy.

Several tests have been proposed as determinants of outcome, such as the presence or absence of blanching, the depth and size of abnormal vessels on biopsy, making a test patch or doing reflectance spectrophotometry.[11-13] All of these give some indication of the likely outcome but are limited in that they represent only the small, specific area of the lesion studied. Evidently throughout a given lesion there are areas of superficial and deep vessels and constricted and dilated vessels, with differences so dramatic that predictive studies in one area of the lesion may be completely invalid for another.[14] In practice, a clinician sorts through patients and treats based on the application of one or more of these selection criteria plus clinical experience.

Carefully discussing the probabilities of various outcomes with the patient and family is essential before treatment. In several studies it was found that nearly all patients believe that laser treatment will completely remove all evidence of a lesion without residua of any type.[15] Therefore, the pros and cons of treatment and the probability of an incomplete response should be thoroughly reviewed. Patients should be shown pictures of good, fair and bad results and of scarring.

Because of selective absorption by hemoglobin, argon is the most commonly used laser for treating port-wine stain. Treatment is generally carried out with local infiltration or block anesthesia. The eyes of the patient and the operator should be protected. The power and energy fluency and total energy required are low (1 to 2 W, 20 to 40 J per cm^2). The laser was originally applied in an alternating stripe fashion as a series of contiguous spots.[16] Later techniques have involved continuous application with contiguous lines.[17] The end point is blanching and flattening of the lesion with the epidermis appearing as a clear, white coagulum without gray or black discoloration. Postoperatively, the treated area is covered with a thin film of antibiotic ointment, left open and examined at three- to six-week intervals.

The results of treatment vary rather widely, as judgments relative to reduction in color, absence of color, epidermal atrophy and scarring are highly subjective even when assessed by the same team of experienced operators. In general, however, excellent results (no remaining visible lesion) are noted in 4% to 11%, good results in 54% to 75%, poor or no change in 6% to 12% and scarring in 5% to 21% of patients.[18,19] Figures 3 and 4 are examples of results. The composite results obtained on the last 352 patients treated at the University of Utah are seen in Table 1.

TABLE 1.—*Results of Argon Laser Therapy for Port-Wine Stains in 352 Patients Older Than 12 Years—University of Utah Experience*

Excellent	8%
Good	79%
Poor	9%
Scarring	4%

Perhaps more relevant is the patients' evaluation of the procedure. A recent study indicated that 86% of patients interviewed a year following completion of treatment felt that, while incomplete, "lighter is better," and they would undertake treatment again for results similar to those they had obtained.[20]

The major complications noted are scarring, hyperpigmentation, hypopigmentation and epidermal atrophy (Figure 2).[21] In addition to these, a remaining visible port-wine stain is likewise undesirable. Residual port-wine stains may be treated by a repeat application of argon laser, with a 15% to 20% decrease in color.

Strawberry Hemangioma

Strawberry hemangiomas appear at or shortly following birth and are characterized by an elevated, spongy mass of bright pink tissue. These masses differ from port-wine stains in that as many as 70% will resolve completely. The greatest resolution takes place in the first year, but diminution in size may occur until the seventh year.[22]

Because of a tendency of scarring with laser use in infancy and childhood and a tendency to resolve spontaneously, these lesions are generally observed rather than treated. Treatment with the argon laser is indicated in patients who have the following:

- Ulceration with bleeding,
- Encroachment on body orifices (ear canal, eye, nose, mouth, urethra and anus),
- Destruction of vital structures (tarsal plate, alar cartilage and so forth).

When the argon laser is applied for these indications, the lesion usually becomes ulcerated without bleeding. This is

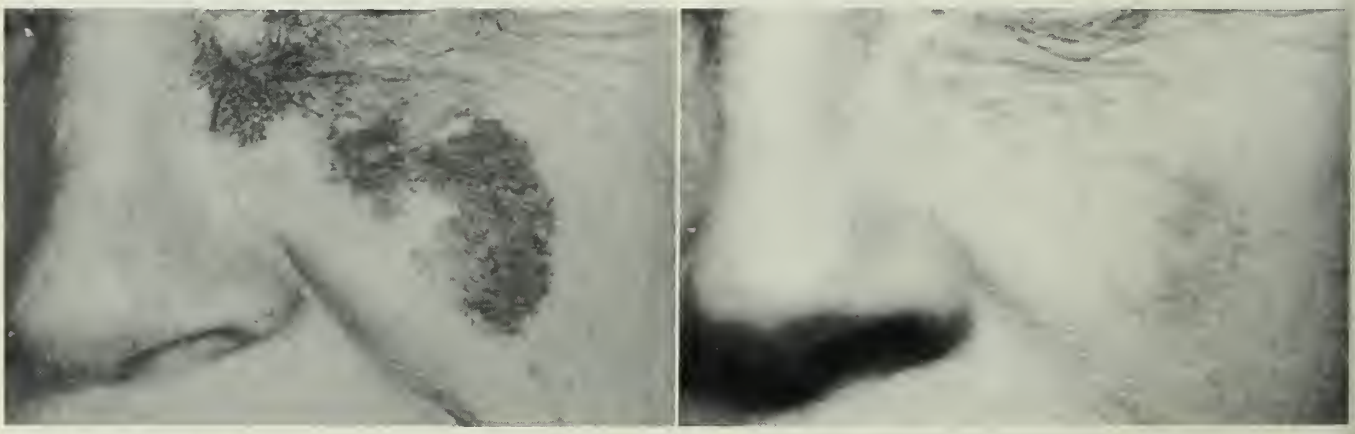

Figure 3.—Left, Dark, slightly nodular port-wine stain, before treatment. **Right,** One year posttreatment with argon laser (1.2 W, 35 J per cm^2), there is good flattening and considerable lightening. No scarring has occurred. The remaining color and spots may be improved slightly by re-treatment in 6 months.

followed by the appearance of gray "herald patches" with beginning resolution. The superficial angioma may then partially or completely disappear. Frequently some of the deeper cavernous portion that is not reached by the argon laser remains.[23]

Laser treatment has been useful where spontaneous resolution of the angioma has left a number of tiny telangiectases in redundant skin present over the angioma.

Pyogenic Granuloma

Pyogenic granuloma is included with the vascular group because of its occurrence in a capillary hemangiomatous plexus in normal skin, port-wine stains or other vascular lesions.

The lesion is primarily a pyogenic infection occurring in a capillary bed. This results in exuberant growth of angiomatous, inflammatory, fibrous and vascular elements.[24] It has a known propensity to recur following surgical excision.

Laser therapy may be accomplished with any of the three common wavelengths. Because of its selective absorption by erythrocytes, the argon laser is probably most effective. Using high power, the lesion is vaporized, including a 1- to 2-mm circumference of normal skin. Any deep dermal ramifications are followed and removed.

Results have been excellent with this form of therapy. Of 11 lesions so treated, there has been only one recurrence; this was minor and easily re-treated.

Telangiectasia

Three types of telangiectasia have been treated, most frequently with the argon laser. The poorest results have been obtained in patients with essential telangiectasia of the lower extremities, such as small varicose veins, spider varicose veins and intracutaneous varices. There appears to be good obliteration of the veins following treatment but in 6 to 12 months remaining or recurrent veins are evident, apparently the result of incomplete thrombosis, recanalization or new vein formation. In our series, only 49% of patients felt there had been any significant improvement from such treatment.[20]

Excellent results have been obtained with argon laser therapy for small, sporadic, punctate telangiectases in the linear vessel ectasia around the malar eminences and over the nose. The small vessel tufts can generally be obliterated by a single application of the argon laser (Figure 5). The linear vessels usually are treated by multiple "spot welds" along the length of the vessel. It may be necessary to re-treat remaining vessels by a second application. Results are generally good, with little scar formation.[25]

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) has been treated with excellent results over the lips, tongue and skin of the face. Again, this is accomplished by using a spot technique with good thrombosis and resolution of the vessels.[26] It is not known why good response is obtained with these abnormalities whereas nonhereditary lesions of the extremities and essential telangiectasia do poorly. This may be due to the difference in hemodynamic factors involving the two regions.

Nonvascular Lesions

Decorative Tattoos

Two types of tattoos are seen—amateur and professional. The amateur tattoo is usually made by putting a drop of india ink on the skin, following which an outline is made by inserting a sharp object such as a needle through the ink into the skin. This tattoo technique results in the insertion of pigment in the dermis, epidermis and even subcutaneous fat. A professional tattoo is generally multicolor with various pigments being used. The pigment is of a much more uniform depth and less frequently involves the deeper layers of the dermis.

Tattoos can be removed with any of the three common laser power sources. In our experience, the CO_2 laser is a bit faster but tends to result in more postoperative pain and a rougher ultimate result. The argon laser is slower but smoother and its use results in less postoperative pain.

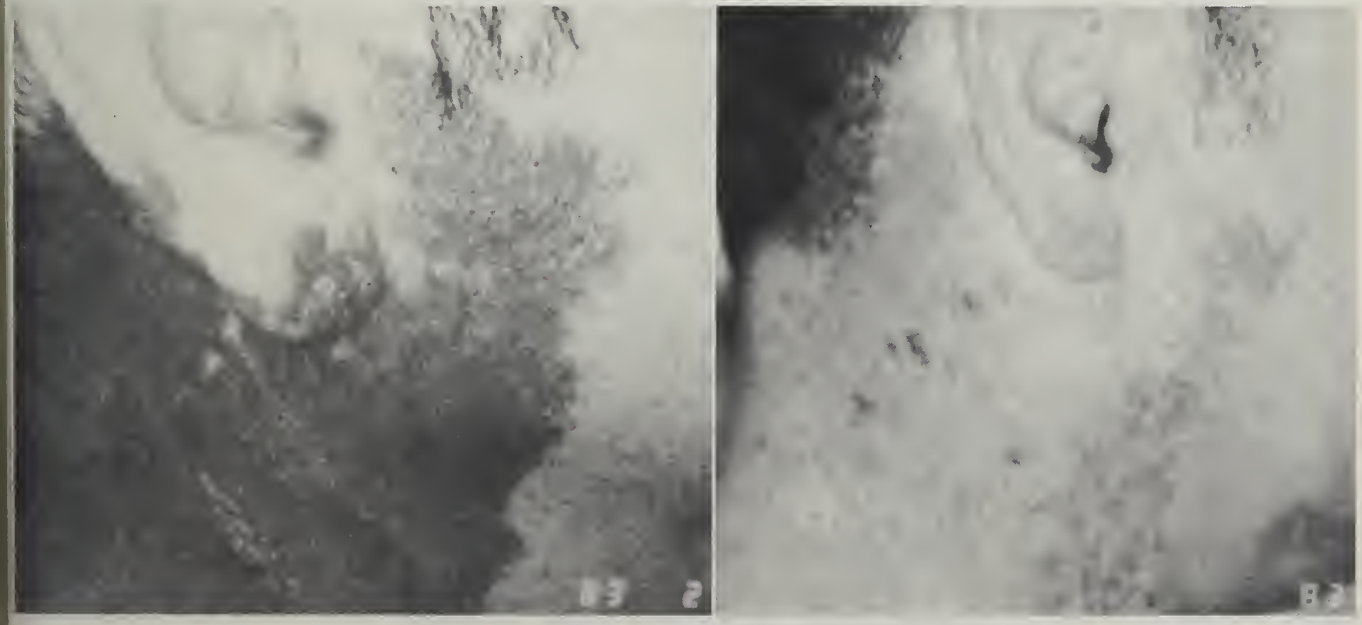

Figure 4.—Left, Dark purple nodular port-wine stain before treatment. **Right,** One year following treatment, there is good flattening and removal of color, with some deep lesion remaining. No scarring is present.

With all lasers, a primary thermal effect is used to coagulate or vaporize. Due to varying depths of pigment, it is necessary to coagulate, vaporize and scrub with saline or hydrogen peroxide. If the pigment is not sufficiently removed, the sequence is immediately repeated.[27] It is sometimes necessary to take three or four layers of pigment and skin off to adequately remove the tattoo. If small areas of pigment deposit are too deep in the dermis, the patient is informed that a subsequent treatment will be necessary rather than risk excessive scarring by continuing.

The results of tattoo removal are good with a high level of patient satisfaction (Figure 6). As might be expected, due to deposition of pigment in the dermis, the incidence of hypertrophic scarring is high, ranging from 12% to 24%. Scarring is most likely to occur with larger tattoos involving flexion or extension creases.

Condylomata

Condylomata are the result of a viral infection and may involve the perianal, vaginal, vulvar, periurethral or penile regions. Previous treatments, such as the use of podophyllum resin, have been extremely painful and followed by recurrence.

Treatment with the laser is best carried out using CO_2 or neodymium-YAG instruments, with a general preference for CO_2. Inasmuch as the virus infection does not extend below the prickle layer of the skin, ablation to this layer is adequate. It is necessary to remove all of the unmistakable condylomata and to use a "superficial brush" technique to remove the superficial layers of the skin around the condylomata, with their concealed pockets of virus. Complete removal is accomplished with one treatment in 75% to 91% of patients and with two or more treatments in 96%.[28] Scarring occurs infrequently.

Warts

Removing common warts can be accomplished with the CO_2 laser. Troublesome plantar and mosaic warts of the foot have also been successfully removed.[29] These techniques are exacting and require careful follow-up with early re-treatment

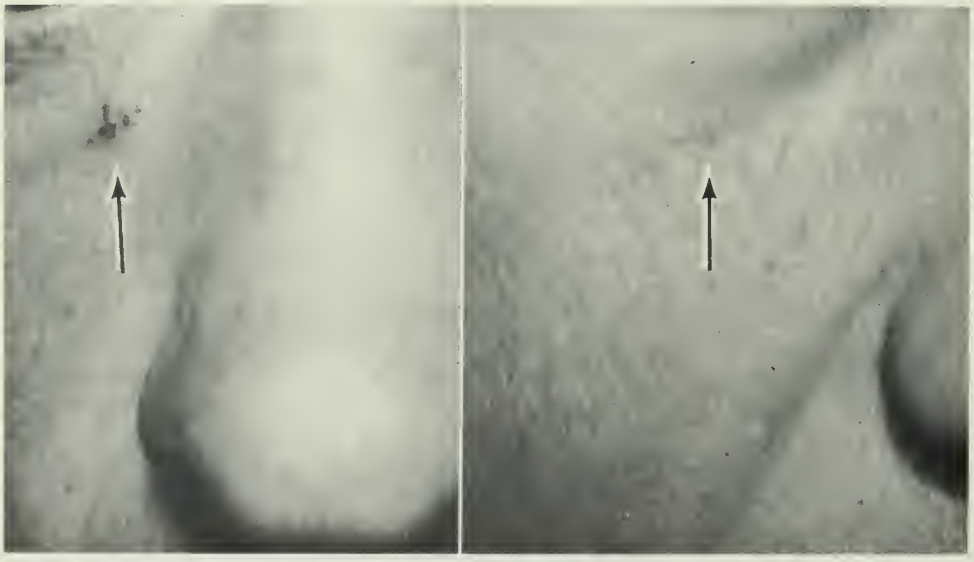

Figure 5.—Left, Small telangiectasis **(arrow)** of cheek, before treatment. **Right,** One year following argon laser therapy, the telangiectasis **(arrow)** has been completely removed.

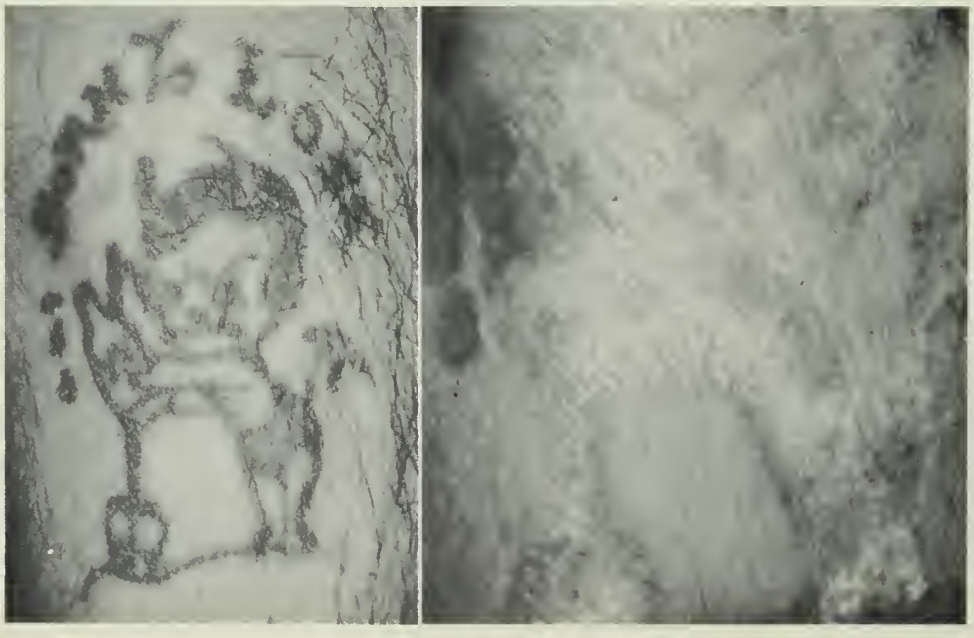

Figure 6.—Left, The photo shows professional tattoo before treatment. **Right,** Three months following argon laser vaporization of tattoo, there is good removal of pigment, with minimal scarring. Some epidermal atrophy is present.

if remaining wart is evident. Pain is less than that following electrosurgical removal of warts.

Excisions and Flaps

The CO_2 laser has been used in most surgical procedures to provide precise excision of skin with reduced blood loss. The CO_2 laser with an articulating arm is used. The latter, unfortunately, limits the flexibility of the instrument so that it is sometimes difficult to get an appropriate plane. The technique appears useful, however.

Bailin has shown the versatility of the CO_2 laser in excising small skin lesions, elevating flaps and in the Mohs chemosurgical technique.[30] This can be done quickly with a good degree of hemostasis where capillary and small veins and arteries are involved. Larger vessels are not well coagulated and present a limitation to CO_2 laser use.

The Future of Laser Treatment

One is left with the impression that laser therapy for skin lesions is a very useful but as yet imperfect and evolving technique. Certainly the results of treatment of port-wine stain, tattoos, condylomata, telangiectasia and the like represent significant advances over existing techniques.

The problems of incomplete removal and scarring remain, however. More complete removal of vascular lesions may be achieved by using different wavelengths such as the yellow 577 nm with a pulse modification that produces intense selective vasculitis.[4] Greater selectivity of the destruction of vessels or pigment would be very helpful in this regard.

Scarring may be reduced by using different wavelengths and altering pulse characteristics. In some cases, such as in removing a tattoo, careful attention to postoperative care to prevent infection and decrease fibrous deposition may be useful.

Reflectance spectrophotometry combined with computerized techniques to provide on-line monitoring of skin changes during therapy may likewise be helpful in reducing the total energy applied to the skin when removing a given lesion. In some cases, changes occur faster than an operator's response time and result in an excess of energy deposition and subsequent scar.

Lasers themselves are becoming smaller and more portable, flexible and easier to use. Argon lasers providing up to 2 to 3 W of power and CO_2 lasers providing up to 8 W of power would be adequate for most dermatologic purposes. A number of designs of this type are on the market.

Tunable lasers adjustable to wavelengths appropriate for any particular pigmented or vascular lesion are still in the future. Existing tunable units such as the free electron laser are very large and bulky and not generally available at this time.

The use of chemical agents to sensitize specific tissue by either systemic or topical application may provide considerable advances in this field. Hematoporphyrin derivative is being studied extensively in this regard and shows promise for treating lesions such as multiple basal cell carcinomas.[31] Topical applications facilitated by penetrants such as laurocapram (Azone) are likewise being investigated.[32]

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Cardiac Positron Emission Tomography

EDWARD M. GELTMAN, MD, *St Louis*

Positron emission tomography (PET) is a new technique for noninvasively assessing myocardial metabolism and perfusion. It has provided new insight into the dynamics of myocardial fatty acid and glucose metabolism in normal subjects, patients with ischemic heart disease and those with cardiomyopathies, documenting regionally depressed fatty acid metabolism during myocardial ischemia and infarction and spatial heterogeneity of fatty acid metabolism in patients with cardiomyopathy. Regional myocardial perfusion has been studied with PET using water, ammonia and rubidium labeled with positron emitters, permitting the noninvasive detection of hypoperfused zones at rest and during vasodilator stress. With these techniques the relationship between perfusion and the metabolism of a variety of substrates has been studied. The great strides that have been made in developing faster high-resolution instruments and producing new labeled intermediates indicate the promise of this technique for facilitating an increase in the understanding of regional metabolism and blood flow under normal and pathophysiologic conditions.

Geltman EM: Cardiac positron emission tomography, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:764-772)

During the past three decades, great progress has been made in cardiology with the acquisition of substantial new insights into the physiologic processes of the normal heart and the pathophysiologic processes underlying a wide spectrum of cardiovascular disorders. These advances could not have been made without the development of new invasive and noninvasive techniques, including cardiac catheterization, coronary angiography, echocardiography, Doppler ultrasonography, gated blood pool imaging and thallium 201 scintigraphy. Despite these advancements, the quantitative assessment of regional myocardial metabolism and perfusion has been elusive.

Echocardiography, cardiac catheterization, cardiac computed tomography and magnetic resonance imaging all provide critical information on cardiac structure and mechanical function, but only indirect measures of myocardial perfusion and metabolism. The accurate assessment of regional myocardial perfusion still eludes us. Coronary angiography provides a clear image of the degree of obstruction of the epicardial coronary arteries, but does not provide a quantitative measure of tissue perfusion. Tissue perfusion is determined partially by the severity of a single coronary stenosis, but also depends on the number and severity of stenotic lesions in sequence, coronary perfusion pressure, the presence and patency of collateral vessels, left ventricular diastolic pressure and wall tension and innumerable other factors not assessed during coronary angiography. Coronary sinus catheterization that includes the assessment of total coronary sinus blood flow by thermodilution techniques or coronary arteriovenous differences in content of oxygen, lactate and other substances may assist in evaluating global coronary blood flow and myocardial metabolism. Unfortunately, these measures do not provide the regional information critical to the understanding of atherosclerotic cardiovascular disease, in that there is an unavoidable admixture in the coronary sinus and great cardiac vein of blood emanating from normal and abnormal regions of the heart.

Scintigraphic techniques using single photon-emitting radionuclides have been employed for assessing myocardial perfusion and metabolism. The most commonly used scintigraphic marker of myocardial perfusion has been thallium 201. In experiments during acute ischemia in animals, the myocardial distribution of ^{201}Tl is roughly proportional to flow. The relationship is not linear at very high flows, however. With prolonged ischemia ^{201}Tl accumulation is disproportionately low in ischemic zones. Over several hours following the intravenous administration of a single dose of thallium 201, the distribution of tracer changes, with apparent accelerated disappearance from normal zones and accumulation in or slow disappearance from ischemic but viable zones. These complexities are compounded by difficulties with the quantitative assessment of regional tissue content of

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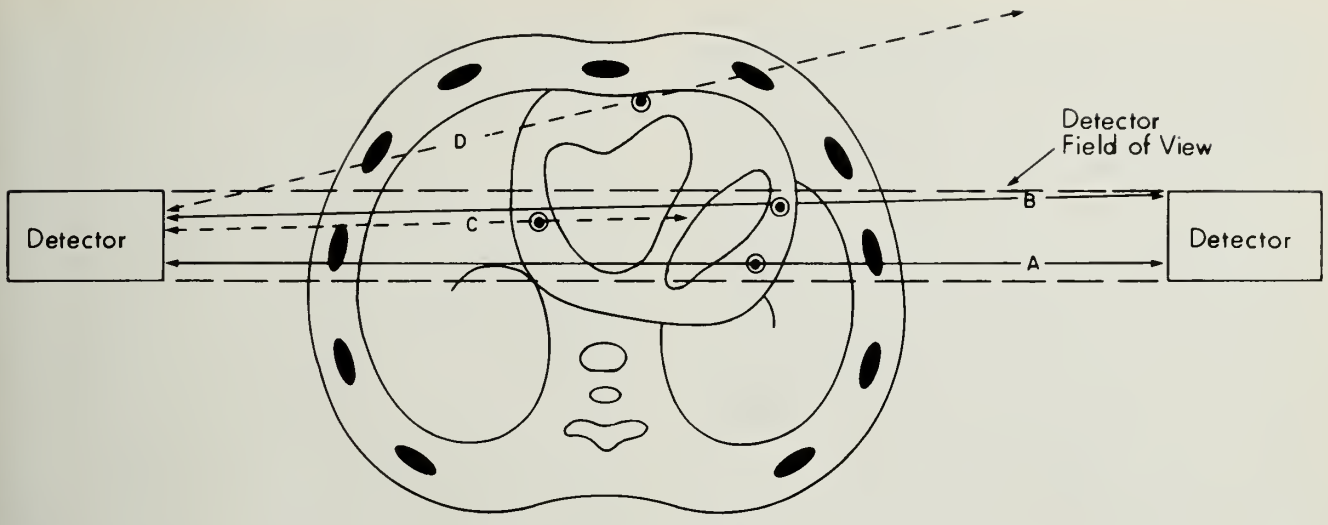

Figure 1.—Each event labeled A through D represents the annihilation of a positron and an electron, forming two γ-photons. Events labeled A and B would be included in a positron-emission tomographic reconstruction, since both γ-photons released from each event reached the detectors. Neither event C nor D would be included in image formation, since only one of each pair of photons reaches a detector. (Reproduced with permission from Geltman and Sobel.[1])

ABBREVIATIONS USED IN TEXT

PET = positron emission tomography
SPECT = single photon-emission computed tomography

TABLE 1.—*Positron-Emitting Tracers*

Isotope	*Half-Life*	*Isotope*	*Half-Life*
Oxygen 15	2.03 min	Fluorine 18	110.00 min
Nitrogen 13	9.98 min	Rubidium 82	75.00 sec
Carbon 11	20.40 min	Gallium 68	68.30 min

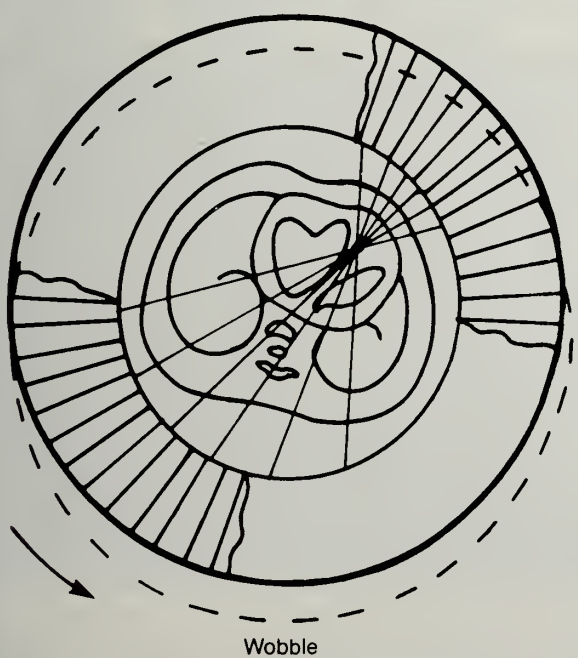

Figure 2.—Schematic representation of a positron-emitting tomographic device constructed as a ring of radiation detectors surrounding a patient. The detector array rotates off axis (wobbles) to increase angular sampling. Representative coincidence lines (lines of photon travel) are indicated.

single photon (γ) emitting radionuclides like ^{201}Tl. Routine studies of single photon-emitting radionuclides depend on two-dimensional representations of three-dimensional events with an unavoidable superimposition of tracer emissions originating from different depths within a patient. The apparent regional myocardial content of radioactivity also depends on the absorption (attenuation) of the γ-photons emitted from the tracer by the intervening structures. This attenuation is dependent on the energy of the γ-photons, the depth of the emitter and the nature of the tissue between the source and the radiation detector. Even when images are acquired from many angles and reconstructed using tomographic techniques (single photon-emission computed tomography [SPECT]), the reconstructed images do not compensate for variable attenuation as a function of depth and tissue density. Thus, despite the clear visual appeal of SPECT images, there are intrinsic limitations to their quantitating capabilities.

Positron emission tomography (PET) is a technique that obviates many of the problems inherent in assessing myocardial perfusion and metabolism with single photon emitters. This is accomplished by exploiting the unique physical characteristics of radionuclides, which decay by emitting positrons. A positron is a subatomic particle with the mass of an electron but a positive charge. When a positron is emitted in tissue, it travels only a very short distance (1 to 3 mm) before it interacts with an electron. In that interaction both particles are annihilated and their mass converted to energy ($E = mc^2$) in the form of two photons (Figure 1),[1] each with an energy of

TABLE 2.—*Positron-Emitting Compounds (Cardiovascular)*

Markers of Metabolism	*Indicators of Blood Flow*
Palmitate ^{11}C (fatty acids)	Ammonia ^{13}N
Deoxyglucose ^{18}F	Rubidium ^{82}Rb
Glucose ^{11}C	Water ^{15}O
Amino acids ^{13}N	Microspheres ^{68}Ga
Pyruvate ^{11}C	*Blood Pool Indicators*
Acetate ^{11}C	Carbon monoxide ^{11}C
	Carbon monoxide ^{15}O

511,000 electron volts. To maintain momentum, these two high-energy γ-photons travel in opposite directions. It is the paired 511 keV γ-photons that are detected in a PET device.[2]

Although the device can be structured many ways, most current PET cameras are structured as one or many rings of radiation detectors, with sophisticated timing circuits (Figure 2). For an event to be included in the ultimate reconstruction, both γ-photons must be detected virtually simultaneously, nearly guaranteeing that the photons detected resulted from a single annihilation event. Because both photons must be detected, the number of coincidence events observed depends primarily on the total attenuation of the absorbers in the cylinder of tissue between the paired detectors, rather than primarily on the position of the radiation source. Furthermore,

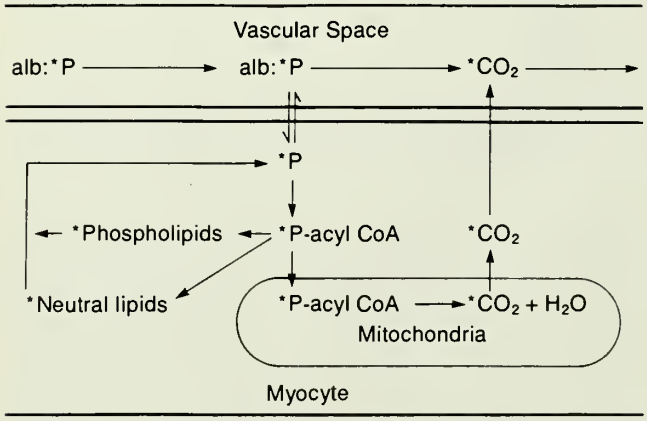

Figure 3.—This diagram shows the potential pathways of palmitate labeled with carbon 11 (*P). Palmitate is transported in plasma, bound to albumin (alb:*P). The tracer (*) has several fates. It may diffuse out of the cell as unchanged palmitate ^{11}C or as carbon dioxide ^{11}C ($^*CO_2$) after β-oxidation. Alternatively, it may be stored as neutral lipid or phospholipid. CoA = coenzyme A (Reproduced with permission from Bergman et al.[2])

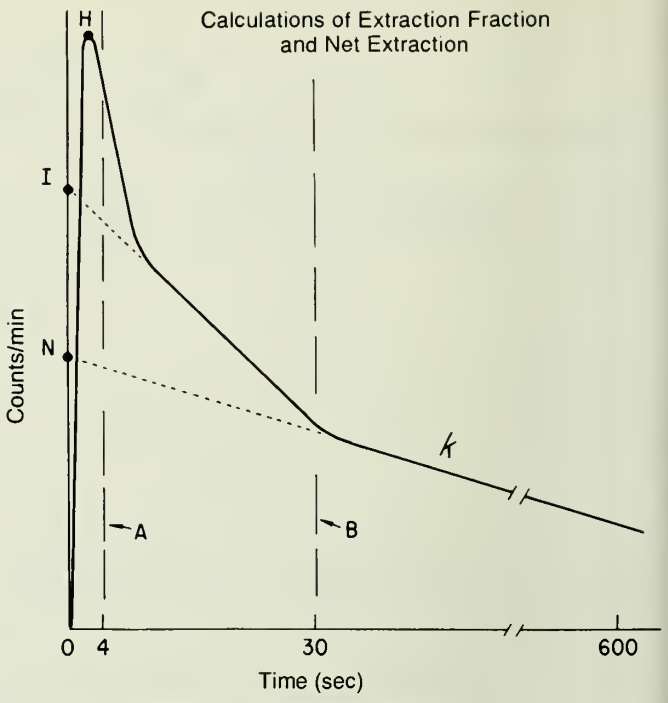

Figure 4.—Schematic representation of a time activity curve recorded after the injection of palmitate tagged with carbon 11 into the aorta of an isolated perfused heart. Peak activity occurs within seconds of injection, followed by vascular clearance of unextracted tracer. Monoexponential clearance is noted (primarily due to β-oxidation). Back extrapolation indicates the amount of tracer extracted from the circulation. The later monoexponential phase represents the slow turnover in the neutral lipid and phospholipid pools. H = peak tracer content of the heart; I = the intercept of the back extrapolation of the vascular clearance to the time of peak activity extraction fraction of tracer into the metabolically active pool = N/H; k = the disappearance rate of the monoexponential phase; N = the intercept of the back extrapolation of the monoexponential phase of β-oxidation to the time of peak activity (Reproduced with permission from Sobel.[3])

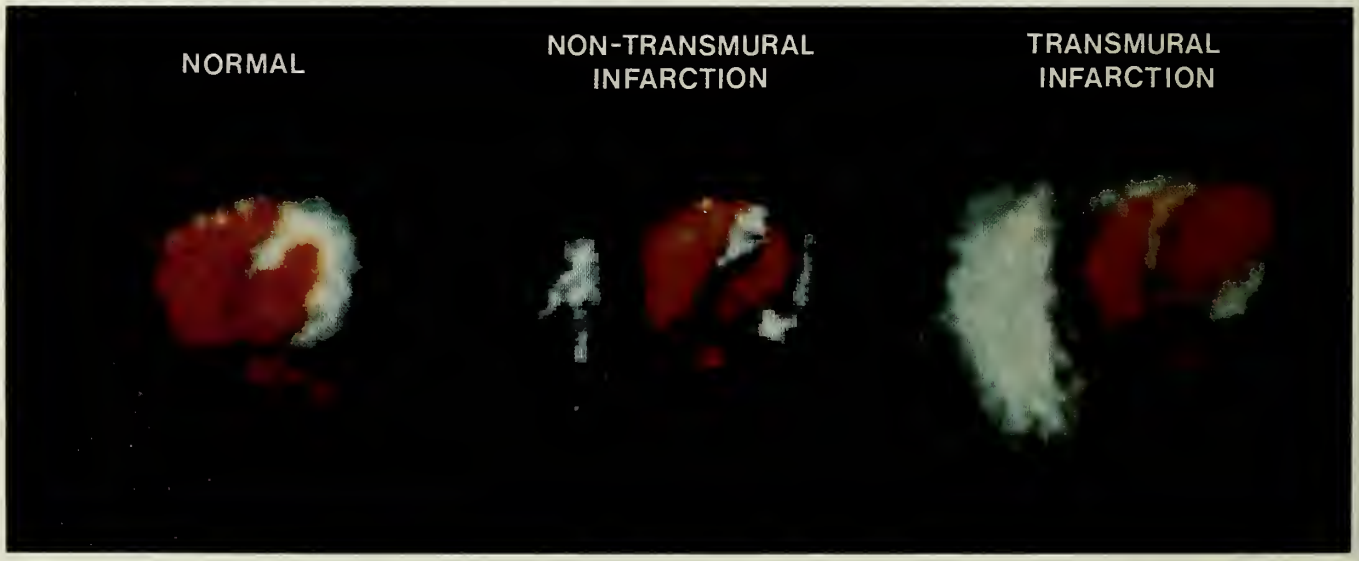

Figure 5.—Transaxial reconstructions from a normal subject and patients with nontransmural and transmural infarction. Data acquired after the intravenous injection of palmitate labeled with carbon 11 are depicted in green, and those acquired after the inhalation of carbon 11-labeled carbon dioxide to label the blood pool are depicted in red. In normal subjects, apparent accumulation of palmitate ^{11}C is homogeneous throughout the heart. The top of each image is anterior and the left of each image represents the patient's right. At this level there is a discontinuity posteriorly because the mitral valve apparatus and atria extract little palmitate ^{11}C and are thin and below the resolution of the instrument (PETT-IV). A dense homogeneous defect in the accumulation of palmitate ^{11}C is evident anteriorly in the patient with transmural infarction. The defect is less dense and less homogeneous in the patient with nontransmural infarction. (Reproduced by permission of the American Heart Association, Inc, Bergmann et al.[4])

the attenuation coefficients can be measured by studying the patient after positioning a thin ring source of a positron emitter in the camera. The attenuation coefficients are used later for correcting data collected after administering a positron-emitting tracer to the patient.

Current generation instruments can achieve a resolution of 7 mm (full width, half maximum) in the plane of section by using extremely fast timing circuits that measure the difference in arrival time of the paired photons at opposite detectors. This "time-of-flight" detection permits the improvements in signal-to-noise ratio necessary to achieve the high resolution critical for the accurate assessment of regional cardiac metabolism and perfusion.

A number of radioisotopes are available for use in PET (Table 1). The short half-lives of these isotopes provide a great advantage for studying rapidly changing biologic events, such as angina and myocardial infarction, because repeat studies can be done in rapid succession. The use of these isotopes (oxygen 15, carbon 11, nitrogen 13) requires a close proximity between the imaging device and the cyclotron required for radionuclide production. Recently, generators have been developed for producing gallium 68 and rubidium 82, tracers that may prove useful for some cardiac applications, possibly obviating the need for a cyclotron with its attendant installation, personnel and operating costs.

Various biologic substances have been labeled with positron-emitting isotopes (Table 2). The labeled compounds used in cardiology have been designed to trace normal and abnormal myocardial lipid and carbohydrate metabolism and to assess regional myocardial blood flow. Ultimately, the number of compounds labeled with these isotopes will be much larger because virtually any biologic substance can be labeled with carbon 11, oxygen 15 or nitrogen 13. Labeling with these radionuclides has the added advantage that the traced substance behaves comparably with the parent nonradioactive compound.

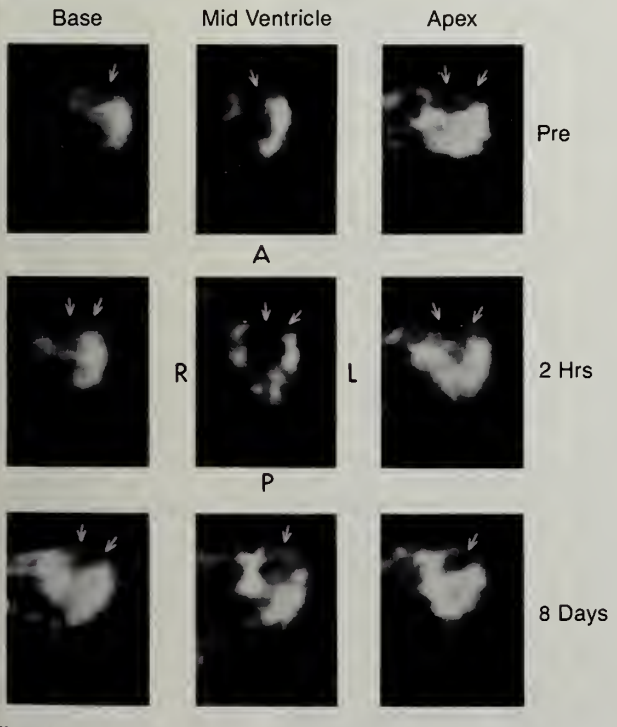

Figure 6.—Positron emission tomographic reconstructions from three levels of the heart taken after the intravenous injection of palmitate labeled with carbon 11 in a patient with an anterior infarction **(arrows).** Data were acquired before administering streptokinase intracoronarily and 2 hours and 8 days after successful thrombolysis. Although the metabolic defect changed little immediately after lysis, there was late return of metabolic activity, indicated in the bottom three panels.

Assessing Myocardial Metabolism With PET

The availability of PET and metabolic substrates labeled with positron emitters has made assessing myocardial metabolism feasible. The detection of the regional myocardial content of tracers is substantially more accurate with PET than with single photon detection methods, but remains a formidable task because regional quantification is complicated by cardiac and respiratory motion, limited resolution (of the same order of magnitude as the objects imaged) and spillover of radioactivity from the cardiac blood pool to the myocardium. All currently available PET devices have a tendency to underestimate actual tissue radioactivity in objects less than twice the size of the minimum resolution element of the instrument (partial volume effect). Because the normal left ventricular wall is only 1 cm thick in diastole, less than twice the thickness of the resolution of any currently available PET system, the apparent radioactivity of regions of myocardium will always represent an underestimate of actual tissue radioactivity unless corrections are applied regionally for myocardial wall thickness.

Additional complexities are encountered when potential metabolic pathways of the heart are considered. Myocardium can utilize a wide variety of metabolic substrates including fatty acids, ketones, glucose, pyruvate, lactate and amino acids. The substrate used by myocardium depends on blood

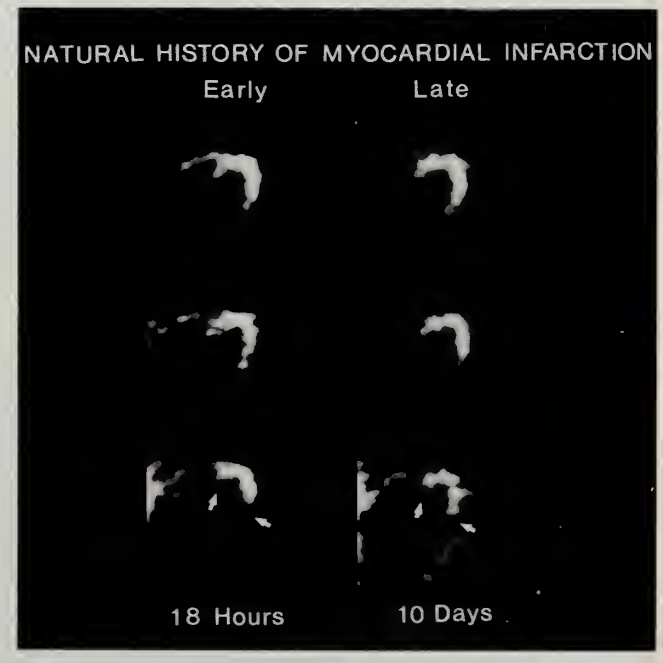

Figure 7.—Positron emission tomographic reconstructions at three levels of the heart (**top,** base; **middle,** midventricle; **bottom,** apex) early and late after infarction in a patient with infarction of the posterior septum and posterolateral walls **(arrows).** There was no apparent change in the distribution of the metabolic defects over the 10-day period shown.

flow, metabolic state, energy requirements and substrate availability in addition to other factors.[2] Hence, the behavior of a single labeled substrate only provides a partial insight into the metabolic state of the tissue.

Under normal conditions, free fatty acids are the preferred substrate of the myocardium, accounting for 40% to 80% of energy production. Fatty acids are transported in plasma bound to albumin. Their extraction by myocardium depends on the albumin-fatty acid ratio, the concentration of fatty acid in plasma and the chain length and degree of unsaturation of the specific fatty acid. Under most physiologic conditions, palmitic acid makes up a substantial proportion of circulating

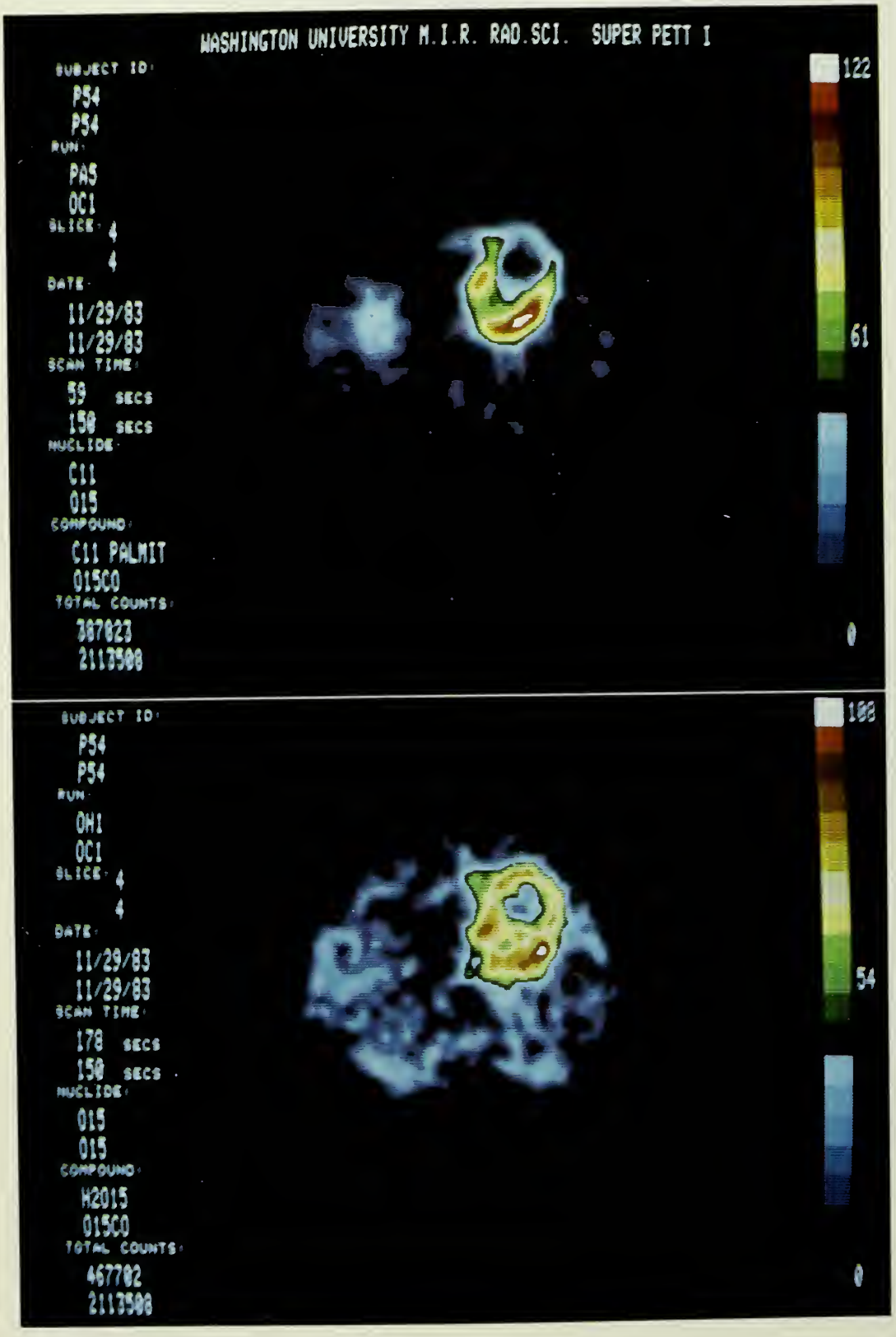

Figure 8.—Top, Distribution of palmitate labeled with carbon 11 as detected with the Super PETT-I in a patient with an anterior infarction showing spontaneous recanalization of the left anterior descending coronary artery noted on angiography late after infarction. White represents the most intense tracer accumulation, blue the least. An anterior metabolic defect is evident. **Bottom,** The distribution of perfusion at the same level of the heart, indicating persistent perfusion in the zone of prior infarction.

fatty acids and accounts for approximately 50% of all myocardial energy production derived from fatty acid oxidation.

The transportation of fatty acids from plasma to a cardiac myocyte is not well characterized, but once a fatty acid moiety has reached the cytosol, it may have several fates (Figure 3).[2] It may simply diffuse back into plasma in unmodified form. The percentage of fatty acid that back-diffuses depends on the general metabolic state of the tissue, with an increase in back-diffusion during ischemia.[2] For fatty acids to be further metabolized, they must be thioesterified in the cytosol. These fatty acid thioesters can undergo β-oxidation in the mitochondria, but only after transport into the mitochondria through a shuttle mechanism involving carnitine. Alternatively, the thioesterified fatty acids may be stored as triglycerides or incorporated into phospholipids.

The metabolic fate of palmitate labeled with carbon 11 has been characterized extensively in normoxic, hypoxic and ischemic settings. After bolus injection of palmitate ^{11}C into the aortic root of isolated, perfused rabbit hearts or the coronary arteries of dogs, the time activity curves show several monoexponential phases (Figure 4).[3] The first reflects vascular washout of nonextracted tracer; the second reflects primarily β-oxidation (although some back-diffusion of unmetabolized tracer is observed during this interval), and the last phase represents slow turnover in triglyceride and phospholipid pools.

During ischemia the extraction and β-oxidation of fatty acids by myocardium decreases due in part to limited myocardial pyruvate. Lack of unesterified coenzyme A limits the thioesterification of fatty acids, decreasing the transport of these species into the mitochondria for β-oxidation. Hence, myocardial cytosolic fatty acid levels increase as does the level of α-glycerol phosphate, which accumulates because of increased glycolytic flux. This combination favors the storage of fatty acids in triglycerides.[2]

These events are reflected externally in hypoperfused myocardium as an increased extraction fraction in a preparation where the work is kept constant (by an external control mechanism) or by a decreased extraction fraction in an uncontrolled model of ischemia (due to decreased extraction matching decreased myocardial work). The clearance of the extracted tracer is slower in ischemic than normoxic myocardium due to decreased carbon dioxide ^{11}C production from β-oxidation, despite increased back-diffusion of unmetabolized palmitate ^{11}C. Even if studies are done by infusing hypoxic blood directly into a coronary artery of a dog during an open-chest procedure at a normal flow rate, the extraction fraction of palmitate ^{11}C and the production of carbon dioxide ^{11}C are greatly reduced, indicating that the abnormalities are not due merely to limited tracer delivery.[2]

Despite the complex behavior of tracers of myocardial fatty acid metabolism in experimental animals, palmitate ^{11}C has proved a useful myocardial imaging agent in patients. Normal subjects have shown homogeneous myocardial distribution of tracer. In contrast, patients with transmural infarction show regions of depressed accumulation of palmitate ^{11}C.[4] These regions appear as dense homogeneous defects that extend through the entire thickness of the myocardium. Patients with nontransmural infarction are observed to have smaller defects that show less intense depression of tissue tracer content with significant heterogeneity within the defect (Figure 5). When the geometric area and the degree of apparent reduction in tissue palmitate ^{11}C content are considered, myocardial infarct size can be calculated. These tomographic estimates of infarct size correlate closely with infarct size estimates based on analysis of plasma creatine kinase curves.[2] PET estimates of infarct size have proved extremely useful for the assessment of therapeutic interventions designed to salvage ischemic myocardium.[5] When occlusive coronary thrombi in patients were lysed with streptokinase or tissue-type plasminogen activator early after infarction, the size of the zone of decreased myocardial accumulation of palmitate ^{11}C was significantly reduced, indicating metabolic salvage of jeopardized but possibly viable myocardium (Figure 6).[5] When there was no intervention, infarct size remained stable (Figure 7). In contrast, in patients with spontaneous late coronary recanalization, reperfusion could be shown angiographically or tomographically, despite the presence of a persistent metabolic defect manifested by a zone of depressed accumulation of palmitate corresponding to the locus of infarction (Figure 8).

Under normal physiologic conditions, fatty acids are the primary myocardial energy source. When plasma free fatty acid levels are low, however, glucose is metabolized actively. During ischemia, β-oxidation is considerably depressed and glycolytic flux increases substantially as the myocardium becomes dependent on anaerobic glycolysis with an attendant increase in extraction of glucose from plasma. Once glucose is extracted, it may have many fates. It may diffuse back into the plasma, be stored as glycogen, be burned to CO_2 or incorporated into a variety of carbohydrates or proteins.[2]

Glucose transport into myocytes is facilitated by carrier proteins. Once glucose has entered the cytosol, it is phosphorylated in a reaction catalyzed by hexokinase. Insulin facilitates intracellular transport of glucose directly and increases it indirectly by decreasing plasma free fatty acids (which inhibit myocardial glucose use). During ischemia, glucose transport into myocardium increases as glycolytic flux increases. These changes persist for only a modest interval because intracellular accumulation of lactate and hydrogen ions in the reduced form of nicotinamide-adenine dinucleotide depress the activity of several key glycolytic enzymes.[2]

Glucose and pyruvate have both been labeled with carbon 11 and have been used to study myocardial metabolism. Initial studies in isolated perfused rabbit hearts showed increased extraction of glucose ^{11}C in early ischemia, but not if the ischemia was persistent. In intact dogs with myocardial ischemia, glucose use was found to be disproportionately high compared with fatty acid extraction.

Because the possible intracellular fates of the tracer in animals or patients administered glucose ^{11}C are manifold, 2-fluoro-2-deoxy-glucose labeled with fluorine 18 has been well studied. This compound is extracted by myocardium and phosphorylated. The phosphorylated compound is not further metabolized, has very little back-diffusion and is effectively trapped in the cytosol. After intravenous administration of deoxyglucose ^{18}F, accumulation is slow in myocardium, depending on circulating levels of glucose, fatty acids, local delivery and the presence or absence of ischemia. In normal, fed persons, deoxyglucose ^{18}F accumulates

homogeneously in myocardium. In zones of ischemic but viable myocardium, it accumulates avidly. In some patients after myocardial infarction, zones of myocardium that show depressed accumulation of palmitate ^{11}C will accumulate increased amounts of deoxyglucose ^{18}F, indicating the potential viability of these zones with abnormal metabolism.[6]

Although studying deoxyglucose ^{18}F permits the identification of some metabolic abnormalities in heart, interpretation of clinical data acquired after administration of this agent must be cautious. Deoxyglucose ^{18}F does not behave as unlabeled glucose ^{11}C, and, thus, inferences relating to the metabolism of native glucose may be incorrect. Second, substantial delays are required between tracer injection and imaging, precluding an accurate characterization of transient phenomena.

Tracers of both fatty acid metabolism and glucose metabolism have been studied in patients who have congestive cardiomyopathy. The myocardial distribution of palmitate ^{11}C showed pronounced spatial heterogeneity in patients with congestive cardiomyopathy. The patterns observed were similar in patients with cardiomyopathy of varying causes, suggesting that the tomographic findings may well represent a final common pathway of injury in these patients with a resultant admixture of normal and fibrous tissue within the heart.[7] The patterns observed in ischemic cardiomyopathy and Duchenne muscular dystrophy were somewhat different, showing large homogeneous zones of depressed accumulation of palmitate ^{11}C in the former and localized zones of increased accumulation of deoxyglucose ^{18}F in the posterobasal portion of the left ventricle in the latter.[8]

Assessing Myocardial Perfusion

The noninvasive assessment of regional myocardial perfusion has been the goal of many investigators over the past decade. This goal is of considerable importance for the detection of coronary artery disease and the assessment of the distribution and severity of the abnormalities in the patients identified. Furthermore, the ability to assess regional myocardial blood flow accurately would be of immeasurable importance in evaluating therapeutic modalities designed to augment coronary perfusion acutely or chronically, including thrombolytic therapy, angioplasty and coronary artery bypass grafting. In addition, knowledge of regional perfusion is critical to the development of a fuller understanding of the etiology and pathophysiology of regional abnormalities of myocardial metabolism observed in a host of disorders.

Several methods have been used with positron-emitting tracers for evaluating myocardial blood flow. The reference standard for virtually all studies of regional perfusion uses left atrial or left ventricular injection of radioactively labeled microspheres with counting of tissue samples in vitro. This approach has been adapted to PET with the use of macroaggregated albumin labeled with gallium 68 or carbonized microspheres injected into the left atrium of dogs or the left ventricle of patients.[9] Tissue radioactivity assessed with PET correlated well with tissue sampling in animals and with the distribution of abnormalities of coronary anatomy in patients.

The use of this approach assumes that the particles are trapped completely and permanently during their first transit through the tissue, that the radioactivity does not elute from the particle, that the microspheres are adequately mixed with blood (and not clumped) and that limitations of instrument resolution are adequately accounted for in analyzing the data. Although most assumptions have not been seriously violated in those studies, the technique has not achieved wide use in clinical practice as it is invasive, requiring intraventricular injection of tracer. Although no adverse reactions have been reported, there may be a risk to patients because of the possible occlusion of capillary beds with microspheres in the heart or the brain in persons already compromised by inadequate baseline perfusion.

A more widely applied approach was originally proposed by Sapirstein.[10] In these studies, a cation was injected intravenously with the assumption that the tracer was extracted uniformly throughout the organ of interest in proportion to regional blood flow. Thallium 201 is the prototype for this approach. This type of study has been applied with PET using rubidium 82 and ammonia labeled with nitrogen 13.[11-14] This approach has been the most widely used of PET techniques for assessing myocardial blood flow, in part because of its simplicity, requiring only a single intravenous injection of tracer. Unfortunately, the critical assumptions of the model are not satisfied. It is assumed that extraction fraction is not only independent of flow, but also independent of the metabolic state of the tissue. Furthermore, the kinetics of release of the tracer from myocardium are assumed to be independent of the level of regional perfusion and metabolism. Nitrogen 13-labeled ammonia is transported as ammonium ion ^{13}N in blood and is thought to be transported across the sarcolemma in a carrier-mediated and diffusion-limited manner. It is trapped in tissue after enzymatic fixation requiring glutamine synthetase, an enzyme affected by the metabolic (ischemic) state of the myocardium. The first-pass extraction fraction of both ammonium ion ^{13}N and ^{82}Rb are inversely proportional to flow.[10] Tissue extraction of tracer falls off significantly at high levels of myocardial blood flow, commonly achieved in clinical settings. Therefore, although the tracers provide an index of myocardial perfusion, they do not provide true quantification of regional myocardial blood flow.

Nevertheless, both ammonium ion ^{13}N and ^{82}Rb have been used frequently in studies in animals and patients. In normal animals and human subjects, the distribution of both tracers in myocardium is apparently uniform. Zones of acute myocardial ischemia or myocardial infarction exhibit depressed accumulation of tracer. Studies done in patients at rest and with pharmacologic vasodilatation with ammonium ion ^{13}N have shown myocardial regions with relatively normal tracer accumulation at rest and decreased accumulation with pharmacologic stress in zones corresponding to coronary obstructive lesions as modest as 47% of cross-sectional vascular area.[12,13] In some situations, transient reduction in regional perfusion induced abnormalities that persisted despite reestablishment of perfusion. Although this behavior violates the assumptions of the model, it can be exploited to increase the sensitivity of the technique for the detection of the transient ischemia encountered in patients with angina.

A third approach developed by Kety and Schmidt used diffusible tracers.[15] This mathematical modeling approach is an extension of the Fick principle of the conservation of mass. This technique assumes that the tracer is inert and freely

diffusible, and its accumulation in tissue depends on flow. The tissue-blood partition coefficient (solubility) should be constant throughout the organ, and flow is assumed to be constant throughout each region of interest sampled. To fulfill the assumptions of the model, no arteriovenous shunts should be present. This approach has been used with oxygen 15-labeled water for studies of regional perfusion of the brain and heart in experimental animals and in patients.[9,16] The behavior of water ^{15}O is nearly ideal for this purpose. Deviations from the assumptions of the model are slight, as long as regions of interest are kept small (since regional heterogeneity of flow may be encountered at the edges of zones of ischemia). True quantification of regional blood flow with this technique requires arterial blood sampling, but even this requirement can be partially obviated by assessing radioactivity in the cardiac blood pool as an index of integrated arterial tracer delivery.

In experimental animals, the tissue content of water ^{15}O (assessed destructively) correlated with myocardial blood flow measured with microspheres ($r = .94$) over a wide range of flows. When assessed tomographically, water ^{15}O was injected as an intravenous bolus and data were collected over a 40-second interval beginning with the arrival of radioactivity in the left ventricle. Accurate delineation of tissue radioactivity requires correcting for vascular radioactivity, which was accomplished by studying animals following the inhalation of carbon tagged with oxygen 15 to label the blood pool. Data were corrected on a pixel-by-pixel basis for radioactivity emanating from the ventricular and intramyocardial blood pools (Figure 9). Regional blood flow assessed in this manner correlated closely with measurements using microspheres ^{68}Ga assessed in vivo with PET ($r = .93$) or tissue sampling counted in vitro ($r = .95$).[9,16]

The assessment of regional myocardial blood flow with water ^{15}O or carbon ^{15}O has proved invaluable for the assessment of changes in regional perfusion after thrombolysis in experimental animals. Preliminary results of studies in patients are encouraging. In healthy volunteers, myocardial blood flow is homogeneous at rest and matches the pattern of accumulation of palmitate ^{11}C. In patients with remote infarction, zones of apparently decreased perfusion were observed in loci corresponding to infarction. In some patients with prior uncomplicated myocardial infarction but a patent

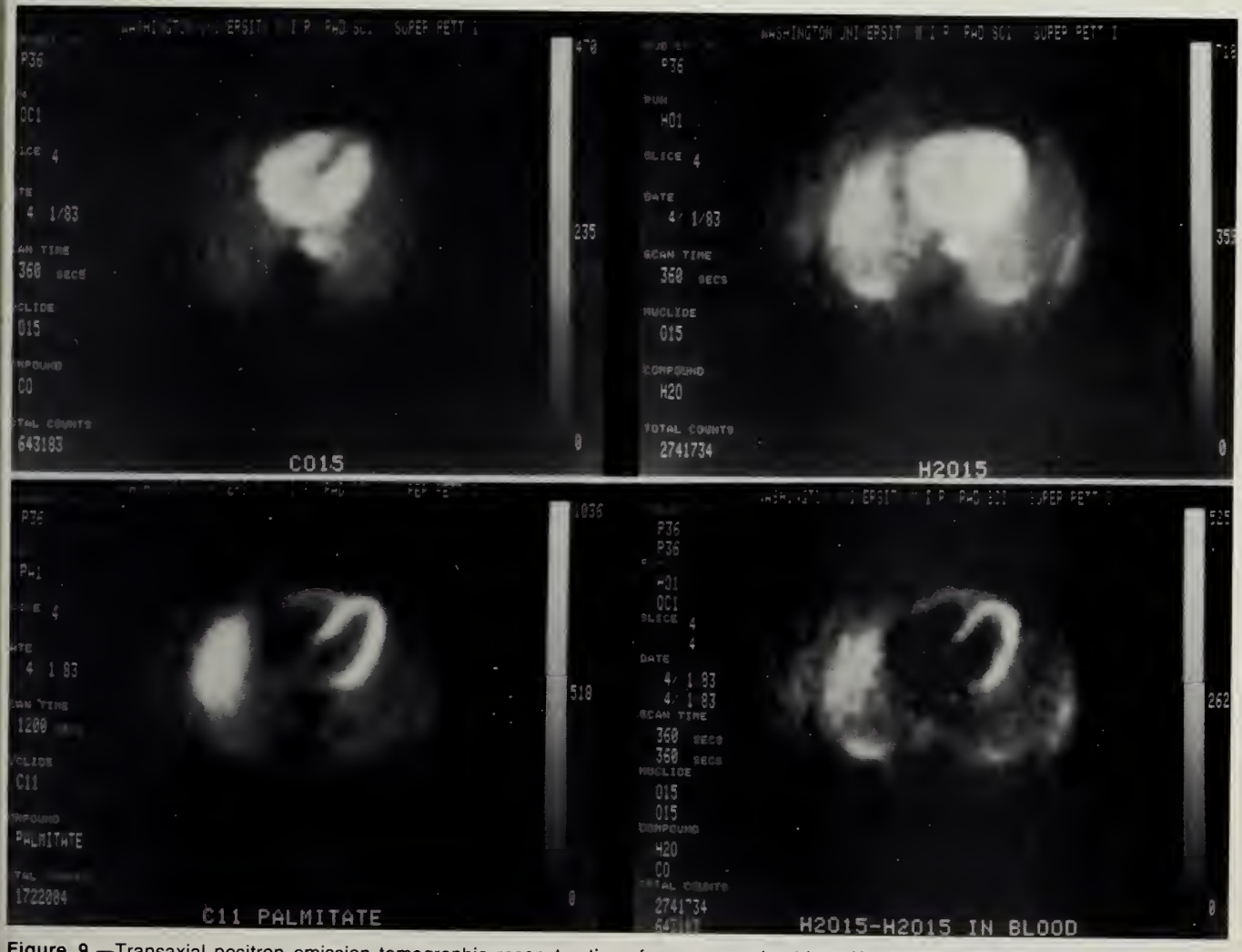

Figure 9.—Transaxial positron emission tomographic reconstructions from a normal subject. **Upper panels,** Reconstructions from data acquired after the inhalation of carbon tagged with oxygen 15 (CO15) to label the blood pool and water tagged with oxygen 15 (H2015) to assess perfusion. **Lower left panel,** The normal distribution of palmitate labeled with carbon 11 (C11 palmitate) in the left and right ventricles and the liver at the same level of the heart. **Lower right panel,** Data from the carbon ^{15}O image were subtracted from the water ^{15}O image on a pixel-by-pixel basis to reconstruct this image of myocardial perfusion.

infarct-related vessel, persistent perfusion was observed in a zone with depressed accumulation of palmitate (Figure 8). This pattern was frequently observed in animals in which reperfusion was initiated late (more than six hours) after the onset of infarction, showing reestablished perfusion despite irreversible metabolic compromise.

Future Directions

Positron emission tomography is a rapidly evolving field with many possible applications in cardiology. Substantial progress has been made in assessing myocardial perfusion and carbohydrate and fatty acid metabolism, yet much remains to be accomplished. Instrumentation is improving at a rapid rate, providing higher spatial resolution and shorter imaging intervals, characteristics that should improve the accuracy of regional estimates of tissue radioactivity and assessment of dynamic metabolic events. Many new tracers are being developed possibly aiding in the assessment of myocardial intermediary metabolism, and protein turnover. The development of receptor ligands labeled with positron emitters (some already used for studies of the central nervous system) should prove invaluable for the investigation of the role of the sympathetic and parasympathetic nervous systems in regulating cardiac function and metabolism. All these developments should help provide a clearer understanding of the pathophysiology of a wide spectrum of cardiac disorders. The progress made so far provides only a small taste of what is yet to come given sufficient industry, insight and support.

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The Current Status of Magnetic Resonance Spectroscopy—Basic and Clinical Aspects

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Magnetic resonance (MR) spectroscopy is a well-established method of chemical analysis in which the magnetic moment and radio-frequency emission characteristics of each atom and molecule are subjected to a high-intensity magnetic field. This method is now established as a noninvasive way of studying metabolism in vivo. With the development of wide-bore, high field (1.5 tesla or above) magnets, studies of human metabolism are now possible. Most metabolic MR spectroscopic studies have focused on the phosphorus 31 nucleus. Spectra can be obtained from phosphorylated metabolites such as adenosine triphosphate, phosphocreatine, inorganic phosphate and sugar phosphate. In addition, ^{31}P nuclear magnetic resonance spectra can provide a continuous monitor of the intracellular pH. The other nuclei used for metabolic studies are hydrogen 1, carbon 13 and, to a lesser extent, sodium 23. Much additional research is required before an assessment can be made of the extent to which MR spectroscopy can be used to provide diagnostically useful information. The noninvasive biochemical approach to human metabolism may involve as-yet-undiscovered metabolic features of disease processes.

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Nuclear magnetic resonance (NMR), a phenomenon in which particular atomic nuclei respond to the applications of magnetic fields by absorbing or emitting electromagnetic radiation, was first demonstrated independently by Bloch and Purcell and colleagues in 1946.[1,2] Further refinement then led to the use of this property for chemical analysis, and its use has spread from the fields of chemistry to biochemistry and recently to biology and medicine. Magnetic resonance (MR) imaging and magnetic resonance spectroscopy are simply two applications of the same phenomenon. In a very short time, MR imaging using protons has become a useful diagnostic technique. With its greater demand on magnetic field strength and homogeneity, MR spectroscopy has been slower to reach clinical utility. MR spectroscopy is, however, an attractive option because some important bodily processes can be monitored at the molecular level.[3,4] The ability of MR spectroscopy to make metabolic diagnoses depends on the continuous measurement of key metabolites, intracellular pH, enzyme reaction rates and ionic activities.[5] During the past ten years, MR spectroscopy has become an accepted new tool in metabolic studies of cells, tissues and isolated organs. Its extension to studies in animals and humans is very recent and depends on the development of the spatial selection of the NMR signals.[6] These studies clearly will be valuable for elucidating certain facets of metabolic processes noninvasively. In addition to its diagnostic potential, the technique of MR spectroscopy may enhance our understanding of fundamental biologic interactions and disease processes.

The objectives of this review are twofold: First, the physical principle of NMR and MR spectroscopic instrumentation will be described. Second, the diagnostic potentials of MR spectroscopy will be examined.

Principle of Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy is essentially similar to other forms of absorption spectroscopy. In principle, all nuclei possess an overall positive charge and some also have a net spin, giving them a magnetic moment. These nuclei may be considered as small magnets spinning on their axes. When

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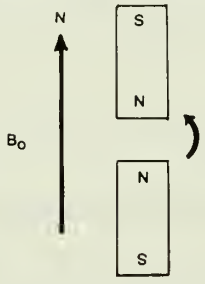
ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
ATP = adenosine triphosphate
MR = magnetic resonance
NMR = nuclear magnetic resonance
T1 = spin-lattice relaxation time
T2 = spin-spin relaxation time

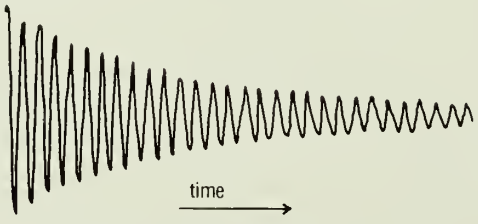
such nuclei are placed in a homogeneous magnetic field of high intensity, they tend to align in specific ways depending on their spin. The nuclei in different orientations have differing energies. Transitions between these energy states can be induced by electromagnetic radiation in the radio-frequency range, which is typically applied as a short pulse. This two-way transition or flipping is a hallmark of the resonance process. The energy absorbed and reemitted by the nuclei induces a current in a suitably tuned coil of wire. The signals are then amplified and displayed as a sinusoidal wave that decays with time. This decay is called a free-induction decay. The initial intensity of the signal is proportional to the number

1. The nuclei of certain elements behave like tiny bar magnets

2. They orient in a magnetic field and can be caused to undergo a transition by a radiofrequency pulse of suitable frequency



3. The transition gives rise to a resonance and can be recorded as a free induction decay (FID)



4. Spectrum after Fourier transformation of the FID

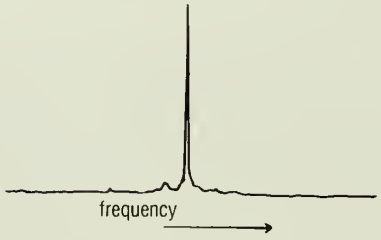


Figure 1.—A simplified explanation of the nuclear magnetic resonance phenomenon.

of nuclei giving rise to the signal, its frequency is a measure of its chemical shift and its rate of decay is related to the transverse relaxation time (T2) of the nucleus. Figure 1 gives a simplified explanation of the NMR phenomenon.

Only those nuclei that have magnetic moments can be observed in this way. Most atoms have at least one isotope with this property, but so far in biomedical research the four most useful nuclei are those of hydrogen (^{1}H), phosphorus (^{31}P), sodium (^{23}Na) and carbon (^{13}C). At a given magnetic field, each of these nuclei will absorb radiation at very different frequencies, the relationship being expressed by the equation

$$\nu = \gamma B_0/2\pi$$

where ν, the absorbed frequency (hertz), depends on the strength of the magnetic field (tesla), B_0, and γ, the magnetogyric ratio, is a characteristic property of the specific nucleus. This relationship allows a spectrometer and coil probe to be tuned onto the frequency of a selected nucleus before each NMR experiment. The chemical environment of the nucleus modifies its local magnetic field, B_{local}. This is conventionally described as

$$B_{local} = B_0(1-\tau),$$

where τ is the shielding constant. As a result, members of the same nuclear species occupying different positions in a molecule resonate at slightly different frequencies. In ^{31}P NMR, the shielding constant has a range of about 40 ppm (parts per million) for biologic phosphates. Using a 1.89-tesla NMR instrument, a sweep of $\pm$2,500 Hz centered about 32.5 MHz (resonance frequency of ^{31}P at 1.89 tesla) will excite the entire range of the phosphate-containing metabolites. This so-called chemical shift allows us to record a high-resolution spectrum in which the signals from different chemicals containing the same nuclei are separated. To remove the dependence of the chemical shift on the magnetic field strength and therefore operating frequency, the chemical shift is usually expressed in terms of parts per million relative to a standard measured along with the sample:

$$\text{ppm} = (\nu_r - \nu_s)/\nu_s \times 10^6$$

where ν_r is the resonance frequency of interest and ν_s is that of the standard. The positions of resonance peaks are measured relative to a standard. It is best to use an endogenous compound that is present in the sample as the standard because it will experience a magnetic environment that should be identical to that of the other substances giving rise to signals. Phosphocreatine or water have both been used in this way. Phosphocreatine is an ideal endogenous reference compound for ^{31}P studies because its peak has a narrow natural line width and its resonance frequency is insensitive to pH changes within the physiologic range. If there is no phosphocreatine signal from a tissue, a useful reference compound is water. Because water protons are present at a concentration of about 80 mol per liter in tissues, they give a signal that can be detected even by a probe tuned for ^{31}P.

In a typical NMR experiment, resonance or transitions between the nuclear orientations can be induced repeatedly by irradiation at the resonance frequency. When the radio-frequency pulse is turned off, the original orientation is restored. The usual frequency spectrum can then be obtained by computing the Fourier transform of the signal-average free-induction decay (Figure 1). The Fourier transform is a mathemat-

ical function that relates a complex waveform to the spectrum of frequencies composing it. Therefore, it is possible to effectively measure the extent to which the radio waves interact with the magnetically polarized nuclei and express it in a form of conventional absorption spectrum. Figure 2 shows a typical ^{31}P NMR spectrum in normal human arm muscle during rest. In this spectrum, we have been able to identify the chemicals that give rise to the individual signals. The areas of the resonance peaks are proportional to the concentrations of the ^{31}P nuclei of those species. The other characteristic property rests in the widths of the peaks. In general, these depend on the mobility of the group concerned. Small unbound molecules will give rise to very sharp peaks, whereas macromolecules or immobilized small molecules will produce very broad signals.

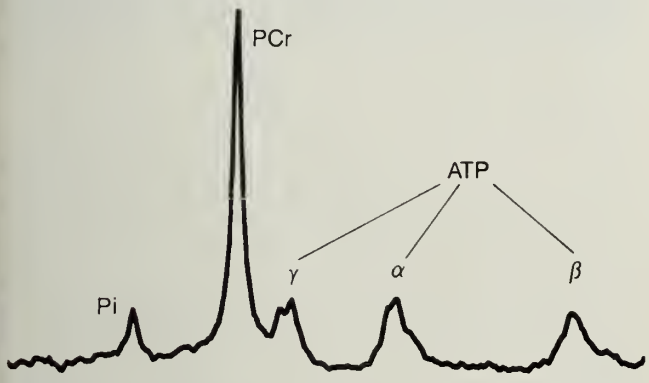


Figure 2.—A typical Fourier-transform ^{31}P nuclear magnetic resonance spectrum of normal human skeletal muscle obtained on placing the forearm adjacent to a surface coil within a wide-bore horizontal magnet as shown in Figure 4. The spectrum was accumulated using 64 pulses applied at 2-second intervals. ATP = adenosine triphosphate, PCr = phosphocreatine, P_i = inorganic phosphate

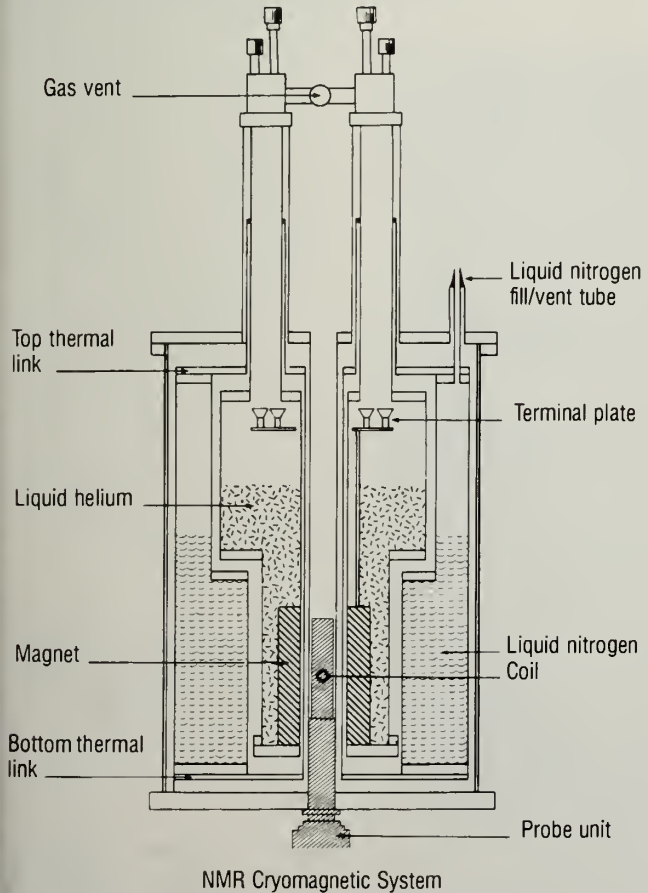


Figure 3.—Schematic diagram of the cryogenic system for a conventional nuclear magnetic resonance (NMR) spectrometer with a vertical-bore magnet. (From Chan.[7])

Instrumentation

There are four essential components for any NMR procedure: a specimen, a magnet to polarize the magnetic nuclei in the sample, a radio-frequency transmitter that supplies the radiation for excitation and a radio-frequency detector that registers the resonance as a change in the specimen's magnetization. Most of the NMR spectrometers in chemical laboratories have vertical-bore magnets with a diameter of less than 8 cm (Figure 3). These conventional NMR instruments, with magnetic fields between 2 and 8 tesla, allow studies on isolated tissues, organs and small animals only. As a result of advances in superconducting magnet technology, horizontal 30-cm-bore magnets have been available since 1980, with fields of up to 1.89 tesla. These instruments can accommodate medium-sized laboratory animals, isolated human organs and human limbs within the bore of the magnet (Figure 4).

During the past several years, technologic advances have permitted construction of magnets large enough to accommodate the entire human body. As a result, clinical studies of humans by MR spectroscopy are becoming a reality. Most of the magnets used for proton imaging in hospital have a field strength of less than 0.6 tesla. To have the capability to do ^{31}P MR spectroscopy, a magnet of at least 1.5 tesla is needed. Two approaches are being used currently for studies in humans. One is to use a medium-bore magnet (20- to 40-cm horizontal bore with a field strength of 1.89 to 2.3 tesla) for selected clinical studies of neonates or human limbs in vivo. It is less expensive to set up this instrument, and it allows laboratory staff to familiarize themselves with the nuances of MR spectroscopy in a clinical setting. The other approach is to install a wide-bore magnet (60- to 100-cm horizontal bore with a field strength of 1.5 to 2 tesla) in a specially designed site for spectroscopy and imaging. The installation of such a high-field clinical NMR with spectroscopic capability should be carefully planned because it represents a major commitment by an institute. There are quite a few centers with such instrumentation and clinical studies are being carried out with the intent of combining spectroscopic with imaging modalities.[9,10]

In traditional MR spectroscopic studies, the signal is obtained from the entire portion of a specimen within the transmitter and receiver coils of the spectrometer. Thus, the sampled region can be quite large and heterogeneous. Conventional spectroscopic techniques are not suitable for most in vivo studies because of the need to localize the signal source to a specific region within the specimen. While imaging has solved the problem of spatial localization, this remains an area of active research in magnetic resonance spectroscopy. The use of surface coils and field focusing in live animals[11,12] has been extended with moderate success to studies in humans. Improved spatial localization, however, has been shown using new surface coil designs and composite pulse sequences.[13-15]

Important Nuclei for MR Spectroscopy in Living Systems

The type of information obtained from any NMR observation is determined primarily by the nucleus selected for detection. The relative sensitivity is different for different nuclei. As a spectroscopic technique, NMR has a low sensitivity. In addition, the ionic conductivity in biologic tissues constitutes a source of electrical loss at the radio frequencies used in NMR. Therefore, only a limited number of nuclei have been found to be relevant and practicable for study by MR spectroscopy. These include phosphorus, hydrogen, sodium and carbon (Table 1). The first three of these are the naturally occurring isotopes, whereas ^{13}C is ordinarily only present at 1.1% abundance. To obtain detectable signals, it is usually necessary to enrich the specimen with ^{13}C-labeled material. Hydrogen 1 is much more sensitive than ^{31}P or ^{13}C NMR; therefore, it can detect metabolites that are present at concentrations of less than 0.2 mmol per liter. Because of their abundance in biologic tissues, ^{31}P and ^{1}H have been most extensively explored and both have yielded signals from intact tissues in humans.[4,6]

Since the early work on whole blood and skeletal muscle, many experiments have been done that show the usefulness of ^{31}P NMR for studying intact biologic systems.[6,7,16] This has to date been the most popular nucleus for NMR studies of metabolism. The special features include the following: the ability to define the content and chemical nature of the phosphorus-containing molecules and follow their transition in time into other phosphorus molecules; the complete nondestructive nature of the measurements, so that repeated determinations can be made, and the capacity to determine intracellular pH.[17] pH measurements are possible because the resonances, inorganic phosphate in particular, are sensitive to the chemical environment of the nucleus observed. The unique features of ^{31}P NMR studies are best shown in Figure 5. In this experiment, the dynamic changes of renal pH and adenosine triphosphate (ATP) concentration in response to changes in systemic blood pressure are depicted. The metabolites observed include ATP, adenosine diphosphate (ADP), phosphocreatine, nicotinamide adenine dinucleotide, inorganic phosphate and sugar phosphate. Intracellular pH is measured by noting a shift in the resonant frequency of the inorganic phosphate peak. Furthermore, ^{31}P NMR can also be used to measure the fluxes of certain enzyme reactions in vivo.[18] This method is called saturation transfer, a type of

TABLE 1.—*Important Biological Nuclei for Nuclear Magnetic Resonance (NMR) Studies*

Nuclei	*NMR Frequency (MHz) at 1.89 tesla*	*Natural Isotopic Abundance*	*Relative Sensitivity*	*Range of Compounds of Biologic Interest*
Hydrogen 1	80.3	99.98	1	Large
Carbon 13	20.2	1.11	1.6×10^{-2}	Large
Sodium 23	8.1	100.00	9.1×10^{-2}	Few
Phosphorus 31...	32.5	100.00	6.7×10^{-2}	Few but important

Figure 4.—The 1.89-tesla horizontal-bore nuclear magnetic resonance spectrometer (TMR-32) being used to study human skeletal metabolism in vivo. (From Ciba Foundation Symposium 87.[8])

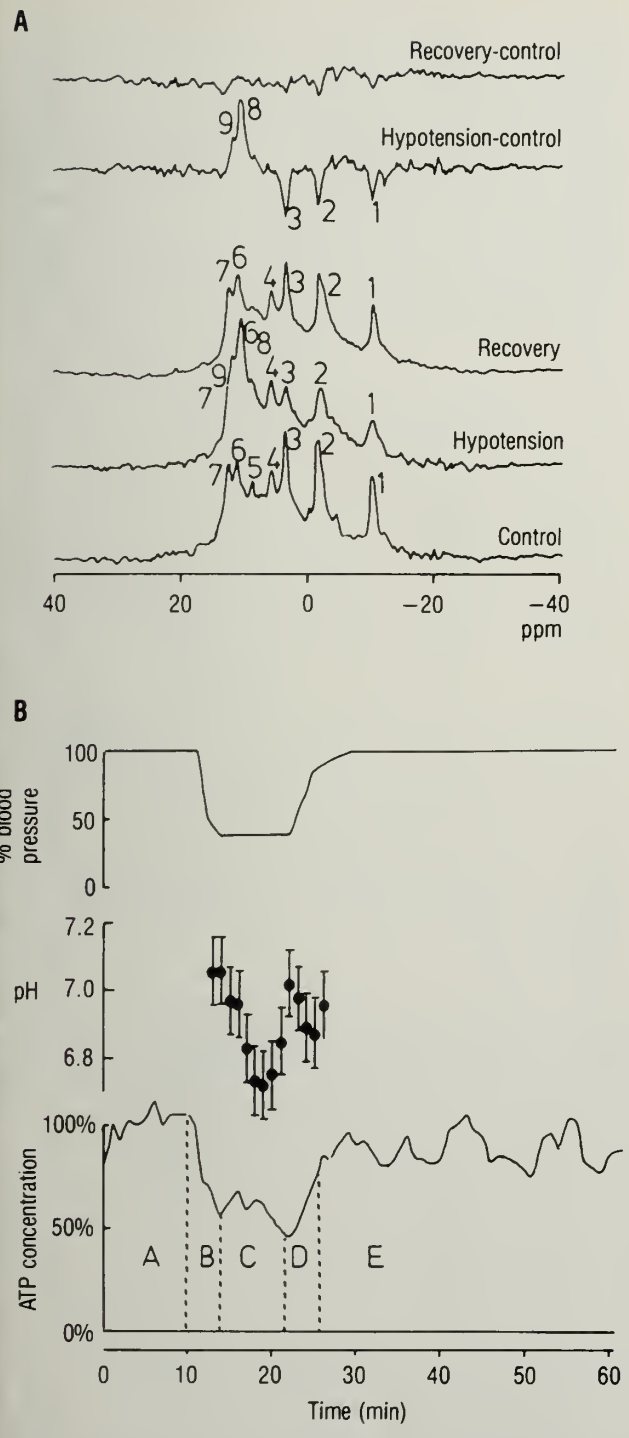


Figure 5.—A, ^{31}P Nuclear magnetic resonance spectra of in vivo rat kidney during hypovolemic shock and recovery. Peak assignments: 1, adenosine triphosphate (ATP) β; 2, ATP α; 3, ATP γ; 4, phosphocreatine (presumably from neighboring skeletal muscle); 5, glycerophosphorylcholine; 6, 2,3-diphosphoglycerate and inorganic phosphate; 7, 2,3-diphosphoglycerate and sugar phosphate; 8, inorganic phosphate; 9, sugar phosphate (such as adenosine monophosphate). Pulse width, 70°; repetition rate, 1 second; exponential line—broadening, 20 Hz. **B,** Time course of pH, ATP concentration and blood pressure (%) during hypovolemic shock and recovery. A, control period; B, 5 ml of blood removed from animal; C, period of hypotension; D, 5 ml of blood returned to animal; E, recovery period. The ATP time course is obtained from an integration across the β-resonance and has been smoothed with an asymmetric triangular convoluting function. (From Chan et al.[21])

magnetic labeling in which the magnetization of one chemical species is perturbed and the perturbation transferred to a second species if the two are in rapid exchange with each other. The rate of interconversion can be obtained from the extent to which the second species is affected. The kinetics of creatine kinase and ATP synthetase have been studied in living animals in this way.[16,19] The results of such studies on isolated organ and intact animals have clearly established the value of ^{31}P MR spectroscopy in biomedical research[4,7,18] and opened new horizons for clinical applications.[6,20]

The multiplicity of the ^{1}H resonances and the narrow range of chemical shifts (about 10 ppm) compared with those in the phosphorus spectrum make it more difficult to obtain well-resolved ^{1}H NMR spectra in living systems at field strengths equivalent to those used in ^{31}P studies. In addition, the hydrogen concentration of water in most tissue is greater than 70 mol per liter, whereas other molecules usually have a concentration of 5 mmol per liter. Therefore, the spectra are dominated by the large water peak, and specialized techniques are needed to suppress this peak. Only recently has proton spectroscopy with water suppression been feasible in humans and this has generated exciting results.[22] Prolongation of T1 (spin-lattice) relaxation times in proton spectra was shown to occur within minutes and to be a more sensitive indicator of cerebral hypoxia than ^{31}P spectroscopy.[23] Lactate levels from solvent-suppressed proton spectra have been shown to rise before the decrease in phosphocreatine levels normally seen with hypoxia in ^{31}P spectroscopy. Using a surface coil placed over a rat skull, cerebral lactate, aspartate, glutamate and γ-aminobutyric acid levels in rat brain have also been monitored during hypoxia and hypoglycemia.[24] Because of the inherently greater sensitivity of proton compared with ^{31}P and ^{13}C, this technique shows considerable promise for in vivo studies in humans.

Although ^{13}C is present at only 1.1% natural abundance (Table 1), ^{13}C studies on intact systems can still be carried out.[25,26] In addition, NMR studies using ^{13}C enrichment can detect the distribution of labeled carbons within a molecule and measure the amount of label at each site. Thus, the metabolism of individual carbon atoms can be followed through enzymatic steps. This approach has been used in isolated cells and perfused organs,[27] and natural-abundance ^{13}C studies have been done in the human forearm. It is possible that this method will be feasible for studying carbon metabolism in humans.

Other nuclei such as sodium 23 and fluorine 19 have been used to study a variety of biologic systems, but the applications are still limited. With the use of a shift reagent, dysprosium tripolyphosphate, the presence of ^{23}Na in intracellular and extracellular sites can be separately determined in isolated tissues and perfused organs.[28,29] Much work needs to be done to test the toxicity of these agents. On the other hand, it is possible to obtain ^{23}Na images of animal models and humans under different experimental conditions.[30,31] In addition to changes caused by ischemia, increased intracellular sodium concentrations are noted by MR imaging in other causes of edema, as well as in mitogenesis and oncogenesis. It is clear that ^{23}Na NMR may turn out to be a very exciting investigative tool. Finally, chemicals labeled with fluorine 19 may provide a useful probe for MR spectroscopy. For example, intracellular calcium can be determined by MR spectroscopy of che-

lators labeled with ^{19}F.[32] In vivo imaging and spectroscopy have also been done in animals treated with fluorinated blood substitutes. It remains to be seen how these approaches can be applied to the study of disease in humans.

Diagnostic Potential

The vast majority of the clinical work on NMR has involved proton imaging. Chemical shift imaging and spectroscopic studies of other nuclei are still very much in a research stage. The first NMR spectrometer suitable for human studies was the TMR 32 (Oxford Research System), with a horizontal bore of 20 cm. This permitted examination of human muscle in adults and clinical studies in neonates. Subsequently, superconducting magnets (1.5 to 2 tesla) with a 100-cm diameter bore and a high-resolution capability have become available. With this size, the entire human body can be examined. There are many unresolved issues that must be addressed, however, before spectroscopy can be used as a clinically useful tool. Issues such as spatial localization and interpretation of spectra have already been studied in ^{31}P MR spectroscopy in animal models. Much has already been learned from ^{31}P MR spectroscopy of the diagnostic potential of the technique, though initial efforts have been concerned with the technical details of acquiring the signals in the correct way and establishing a set of normal values. The studies done so far are summarized in Table 2.

Skeletal Muscle

Most of the studies in human beings have focused on the response of skeletal muscle metabolism to exercise and on pathologic changes in muscle metabolism due to biochemical disturbances. A series of studies, based on the results of ^{31}P MR spectroscopy done in more than 200 patients and healthy controls, established a set of normal criteria.[6,33] A typical series of ^{31}P NMR findings of an exercise regimen are shown in Figure 6. The concentrations of phosphocreatine, adenosine triphosphate and inorganic phosphate, as well as intracellular pH, can be determined from the ^{31}P spectra. The changes in pH that accompany the progressive fall in phosphocreatine during exercise and recovery in the forearm flexor muscle are shown. Similar data for the lower limb were obtained,[34] showing, in addition, that physical training can be assessed from the rate at which the ratio of inorganic phosphate to phosphocreatine increases with increased work load. In a

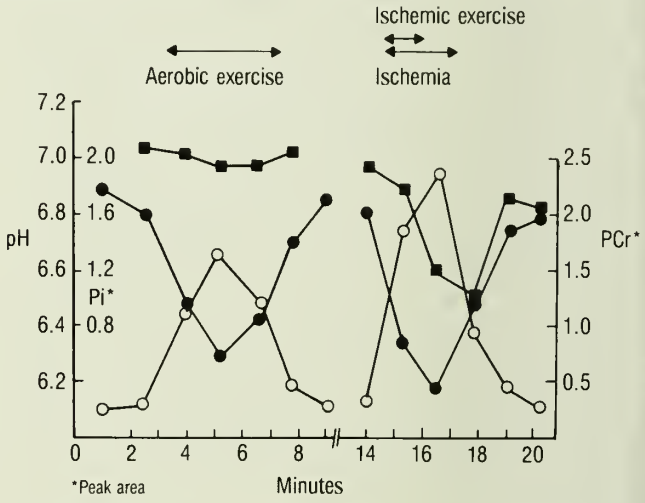


Figure 6.—Exercise-induced changes in normal muscle detected by magnetic resonance spectroscopy using phosphorus 31. Solid squares, pH; solid circles, phosphocreatine (PCr); open circles, inorganic phosphate (Pi); units of peak area, cm^2. (From Ciba Foundation Symposium 87.[8])

TABLE 2.—*Summary of Published Work on Clinical Studies of ^{31}P Magnetic Resonance Spectroscopy*

Organ System	*Study*	*Source*
Skeletal muscle	Normal muscle	Radda et al, 1981[4]; Taylor et al, 1983[33]
	Work load v energy metabolism	Taylor et al, 1983[33]; Chance et al, 1981[34]
	Glycogen storage disease	Ross et al, 1981[35]; Chan et al, 1982[36]
	Phosphofructokinase deficiency	Chance et al, 1982[37]
	Mitochondrial myopathies	Radda et al, 1982[38]; Gadian et al, 1981[39]
	Muscular dystrophy	Newman et al, 1982[40]
	Undiagnosed muscle problems	Radda et al, 1984[6]; Arnold et al, 1984[41]
	Neuropathies	Radda et al, 1984[6]
	Systemic disorders	Radda et al, 1984[6]
	Decreased oxygen delivery	Radda et al, 1984[6]
Brain	Normal cerebral metabolism	Bottomley et al, 1983[10]; Hilton-Jones et al, 1984[42]; Proceedings, 1985[43]*
	Localization by TMR	Hilton-Jones et al, 1984[42]
	Neonates and congenital anomalies	Cady et al, 1983[44]
	Stroke	Welch et al, 1985[45]
Liver	Normal liver metabolism	Proceedings, 1985[43]*; Oberhansli et al, 1985[46]; Maris et al, 1985[47]
	Localization by TMR	Oberhansli et al, 1985[46]
	Fructose metabolism	Oberhansli et al, 1985[46]
Heart	Normal cardiac metabolism	Proceedings, 1985[43]*
	Cardiomyopathy	Whitman et al, 1985[48]
Oncology	Sarcoma	Griffiths, et al, 1983[49]
	Neuroblastoma	Maris et al, 1985[47]
	Hypernephroma	Chan et al, 1984[50]; Ross et al, 1984[51]

*Proceedings of the Society of Magnetic Resonance in Medicine, 1985.[43]

trained subject, the inorganic phosphate level rises less for a given increase in work, indicating better respiratory control.

Disorders of glycolysis. The first clinical study on glycolytic disorders was by Ross and co-workers on a patient with McArdle's disease. The condition was found by observing the failure of ischemic exercise to lower intracellular pH in the forearm muscle of the patient (Figure 6).[35] This was in contrast to the pronounced acidosis observed under these conditions in healthy persons. Four patients with similar phosphorylase deficiency were examined in detail. All the patients showed an increase in intracellular pH in the exercising muscle (flexor digitorum superficialis), whereas normal subjects invariably showed a decrease. The onset of fatigue was not related to a lack of ATP or phosphocreatine, but may be associated with the large concentration of ADP that is generated because of the unusually high pH. ADP was calculated from the creatine kinase equilibrium to be about 200 μmol per liter in the patient's muscles compared with about 50 μmol per liter in exercising control subjects.[36] In the uncommon variant of phosphofructokinase deficiency, rapid and substantial accumulation of sugar phosphate (presumably fructose- and glucose-6-phosphates) was observed during aerobic and anaerobic exercise.[37]

Mitochondrial myopathies. Patients with mitochondrial myopathies were examined by using a similar method as for glycolytic disorders. First, an abnormal recovery of phosphocreatine and pH after exercise was shown in patients with nicotinamide adenine dinucleotide (reduced form)-coenzyme Q reductase deficiency.[38] The reduction in the rate of phosphocreatine resynthesis is presumably associated with slow ATP synthesis. We may expect other blocks in the mitochondrial electron transport chain to produce similar effects. Second, a significantly elevated level of inorganic phosphate was measured in the resting muscle of two patients previously diagnosed to have mitochondrial myopathies.[39] One possible explanation for the increase in inorganic phosphate is that the mitochondria are not fully coupled.

Duchenne muscular dystrophy. ^{31}P MR spectroscopy has also been used to study patients with Duchenne muscular dystrophy.[39] In these patients, the ratio of phosphocreatine to ATP is low and the intracellular pH of resting muscle is significantly more alkaline than in normal persons. Other forms of dystrophy have been studied, but the results obtained from the examination of forearm muscle are not diagnostic.

Postviral fatigue. ^{31}P MR spectroscopy is particularly useful in patients with undiagnosed muscle problems. In a series studied by Radda and colleagues at Oxford, 20% of them showed a deviation from the normal NMR pattern.[6] A significant group of patients show abnormally rapid intracellular acidosis at the early stages of aerobic exercise. The excessive intracellular acidosis of skeletal muscle on exercise was also observed by ^{31}P MR spectroscopy in one patient with the postviral fatigue syndrome.[41] The NMR finding may provide new insight into the mechanism of this disease. We may expect hitherto-unknown disorders of muscle metabolism to emerge in the form of unusual phosphate metabolites, abnormal pH or abnormal response to exercise in any one of the four key metabolites (phosphocreatine, ATP, inorganic phosphate and sugar phosphate) observed regularly in these spectra. The findings of these studies show the way in which ^{31}P MR spectroscopy can aid in the diagnosis of disease in humans.

Muscle changes in systemic disorders. This is an area wherein important biochemical information might be expected from the study of skeletal muscle by MR spectroscopy. In particular, the changes in intracellular pH in various disorders of fluid and electrolytes would provide useful information for diagnosis and assessment of treatment. Muscle abnormalities observable by ^{31}P NMR have been seen in patients with different systemic disorders. Of particular interest are patients with hypothyroidism, hypophosphatemia, hypomagnesemia or uremia. The changes in these conditions may shed new light on the pathophysiology of the diseases.

Brain

^{31}P Nuclear magnetic resonance spectra were obtained from the brains of several infants who had suffered severe intrapartum asphyxia or who had congenital anomalies.[44] The ratio of phosphocreatine to inorganic phosphate was found to increase with clinical improvement. With the availability of total body high-resolution magnets, ^{31}P MR spectroscopy of the normal adult human brain has been done.[6,10,42] Characteristically, the human brain spectrum is dominated by a very prominent phosphodiester resonance. The chemical nature of this phosphodiester peak was characterized by in vitro models using freeze extraction. It was found that most of the phosphodiester signal arises from phospholipids in the brain.[52] Studies were also done in patients with stroke. The phosphodiester resonance was unchanged, but the phosphocreatine and phosphomonoester resonances were decreased.[45] These findings suggest that regional and global metabolic disorders of the brain may be monitored by NMR.

Other Organs

Most of the spectroscopic studies in humans involve the use of a surface coil. The experiment does not provide spatially localized spectra. This means that simply doing ^{31}P MR spectroscopy of the chest, for instance, would not be useful as the relative contribution of the heart and skeletal muscle would not be known. Further improvement in spatial localization is needed for spectroscopic studies of organs such as the heart, liver and kidney. Topical magnetic resonance[12] as a method of localization has been applied to the study of the various organ systems in humans.[42,46] Using the technique of field profiling, localization of NMR signals obtained from the liver can be shown chemically during a standard fructose tolerance test. Within five minutes after infusing 200 mg per kg of fructose in a healthy person, a rapid increase in fructose-1-phosphate and a decrease in ATP and inorganic phosphate in the liver were measured from the ^{31}P spectra.[46] In the case of neonates, it might be acceptable to use a surface coil for studying internal organs. This technique was applied to monitor the energy metabolism of cardiomyopathy in a 6-month-old infant.[48]

Oncology

Because of the size limitations encountered with most NMR instruments, investigation of intact human tumors has been restricted to those present in excised organs[50,51] and sarcoma localized on the dorsum of hands.[49] The first detectable abnormality in high-resolution phosphorus spectra of a

human tumor was made with intact but anoxic hypernephroma.[50] Compared with the adjacent normal human kidney tissue, the tumor had a significantly higher ATP level and a lower pH. This finding was substantiated by direct enzymatic assay on tissue extract. The most probable explanation for the difference between normal and tumor tissue is a high rate of glycolysis under anoxic conditions, similar to a Warburg phenomenon.[4] To study malignant hepatic involvement, two infants with enlarged livers due to neuroblastoma were examined by ^{31}P NMR.[47] An in situ tumor was distinguished from host tissue with NMR and contained higher concentrations of phosphorylethanolamine and phosphorylcholine. It was concluded that ^{31}P MR spectroscopy can be used to detect tumors in situ and to monitor their response to treatment.

Safety

The potential sources of hazard in NMR are related to the effects of the static magnetic field, radio-frequency heating effects and the effects of currents induced either by rapidly switched magnetic field gradients (during MR imaging examinations) or by movement through the magnetic field.[9] Apart from the danger to patients with cardiac pacemakers and the possibility that implanted ferromagnetic objects could be caused to move by a strong magnetic field such as those used for spectroscopy, there is currently no verified evidence for any detrimental effect of a static magnetic field. Strict rules and safety precautions should be applied, however, to any clinical NMR laboratories. Subjects for high-field (above 1 tesla) NMR examination should be carefully selected. Patients with metallic implants, surgical clips and pacemakers should be excluded from the study. In ^{1}H and ^{13}C magnetic resonance studies, broad-band decoupling using higher radio-frequency power than the observed pulse will be necessary to suppress interfering peaks. This may cause adverse effects. Further studies with animal models will be necessary and other safety standards and devices need to be developed. Switched magnetic field gradients are mainly used for imaging techniques and are, therefore, not applicable to spectroscopy.

Recently, the Food and Drug Administration has approved the 1.5-tesla MR imaging systems for commercial use. With the additional appeal for regional spectroscopy, more centers would prefer 1.5-tesla systems. However, siting considerations for high-field NMR instruments for spectroscopy are more complicated than for low-field imaging systems. These have implications for safety, for the performance of the equipment and for the well-being of subjects who will be examined. With any superconducting magnet system, the possibility exists that the magnet may quench in the event a portion of a superconducting wire becomes resistive or a superconducting switch opens. The result of such a quench is that the magnetic field decays rapidly. The energy associated with the current is dissipated as heat, which boils off the helium and nitrogen surrounding the windings. For a whole-body magnet of 1.5 tesla, the field would decay over a few seconds and some 200 cubic meters of gas at atmospheric pressure would evolve mostly in the first few minutes. This gas must be directed away to a vent-system or the room must be large enough to accommodate the gas and still leave enough air volume for respiration. All these are important considerations for MR spectroscopy in humans.

Conclusion

In the past few years the use of MR spectroscopy has rapidly expanded to the study of the biochemistry of living tissue. We are only at the beginning of using this technique to study human metabolism. Even though it has been proved feasible to do spectroscopy on the clinical 1.5-tesla systems currently being installed, how high a field is necessary to be clinically useful is not an easy question to answer. Much additional research is required before an assessment can be made of the extent to which in vivo MR spectroscopy would provide useful diagnostic information. It is important to remember that the full utility of the technique relies on the ability to ask the right biochemical questions.[53] Progress is likely to be made in several directions:

- Further technical developments will enable more experiments to be done using nuclei other than phosphorus.
- The spectroscopic method can be adapted so that chemical shift information can be localized spatially.
- Other NMR variables such as relaxation times (T1 due to spin-lattice interactions and T2 due to spin-spin interactions) can be exploited.
- Determining enzyme flux rate, flow and oxygenation are important areas of application of the method.[43]

It is likely that clinically relevant information from imaging and spectroscopy will be simultaneously available as the technology matures. It would then be possible to combine MR spectroscopy and MR imaging so as to detect the distribution of metabolites within a particular organ and to determine the changes of a particular disease and the response to different treatment modalities.

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Basic Principles of Magnetic Resonance Imaging—An Update

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Magnetic resonance (MR) imaging technology has undergone many technologic advances over the past few years. Many of these advances were stimulated by the wealth of information emerging from nuclear magnetic resonance research in the areas of new and optimal scanning methods and radio-frequency coil design. Other changes arose from the desire to improve image quality, ease siting restrictions and generally facilitate the clinical use of MR equipment. Many questions, however, remain unanswered. Perhaps the most controversial technologic question involves the optimal field strength required for imaging or spectroscopic applications or both. Other issues include safety and clinical efficacy. Technologic issues affect all aspects of MR use including the choice of equipment, examination procedure and image interpretation. Thus, an understanding of recent changes and their theoretic basis is necessary.

(Scherzinger AL, Hendee WR: Basic principles of magnetic resonance imaging—An update, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:782-792)

The first nuclear magnetic resonance image was produced by Lauterbur in 1973[1]; since that time, magnetic resonance (MR) imaging has evolved into a clinically useful, although not yet widespread, imaging tool in diagnostic medicine. In early 1985, at least 200 MR imaging units were operating worldwide, with 70% of the total in the United States. Most of the initial sites were university based, but many of the more recent installations have been in outpatient clinics and independent diagnostic centers. Magnetic resonance imaging units are available from 18 manufacturers,[2] with magnetic field strengths ranging from 0.04 to 2 tesla. Two MR imaging societies have a combined enrollment of 1,500 members and several journal articles on MR imaging are published each month.

The rapid growth in clinical applications has been accompanied by numerous technologic advances in MR imaging over the past few years. These advances have affected imaging techniques, image quality, siting considerations, safety concerns and several other aspects of the clinical applications of MR imaging. Still, many questions remain unanswered, such as the clinical efficacy and cost effectiveness of the clinical applications of MR imaging, the optimum magnetic field strength for imaging, long-term health implications of exposure to intense magnetic fields and the overall fiscal viability of the modality.

Imaging Techniques

The basic principles of MR imaging are discussed in several articles.[3-5] Some of these articles describe the two most commonly used imaging sequences, spin echo and inversion recovery, together with modifications of these sequences that have yielded improvements in the signal-noise ratio, contrast resolution and imaging time. Multislice, multiecho spin-echo imaging has become the major MR imaging technique used for clinical imaging; a standard spin-echo examination includes one set of spin-lattice relaxation time (T1)-weighted images (short repetition time [TR]) and one set of spin-spin relaxation time (T2)-weighted images (long TR).

The spin-echo pulsing technique is shown in Figure 1. In this technique, a 90° pulse is applied to a selected slice of tissue. In response, a free induction decay (FID) signal is induced in the receiver coil with an initial value that is proportional to the longitudinal magnetization of the sample at the time of the pulse. The signal decays with a time constant T2*, which reflects both spin-spin relaxation (time constant T2) and relaxation caused by nonuniformities in the static magnetic field. At a time (TE2) following the 90° pulse, a 180° pulse is applied. This pulse reverses the signal decay caused by inhomogeneities in the field, and an echo signal is produced at a time TE following the 90° pulse. The amplitude of this echo relative to the initial value of the FID is a function of

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ABBREVIATIONS USED IN TEXT

AC = alternating current
CT = computed tomography
FDA = Food and Drug Administration
FID = free induction decay
Gd-DTPA = gadolinium-diethylenetriaminepentaacetic acid
MR = magnetic resonance
T1 = spin-lattice relaxation time
T2 = spin-spin relaxation time
T2* = T2 and relaxation caused by nonuniformities in static magnetic field
TE = echo time
TR = repetition time

the true spin-spin relaxation time, T2, and the echo delay time TE. After a time, TR, the entire spin-echo sequence is repeated. A long TR (longer than T1) is chosen if one wishes to allow all tissues to undergo complete longitudinal relaxation. The signal intensity following the 90° pulse is then independent of T1 because the imaged tissue was fully relaxed before the 90° pulse was applied. If the TR is shortened, the tissue will not have complete longitudinal relaxation, the signal intensity will vary with T1 and the image will contain some T1 weighting. Within this framework, the TE values can also be changed to alter the T1 and T2 weighting of the image.

The optimum values of TE and TR for imaging specific tissues is still relatively uncertain, even though considerable theoretical and experimental work has been directed towards answering this question.[6-8] To eliminate the need for a priori knowledge of the appropriate pulse sequence, techniques have been developed to calculate images for any assembly of characteristics from data obtained at two different spin-echo sequences.[9,10] These images have been shown to correlate well with those acquired using actual pulse sequence.

Multiecho spin-echo images are produced by injecting 180° pulses at times TE, 2 TE, 3 TE and so forth following the initial 180° inversion pulse (Figure 2). From two to eight multiple echoes can usually be obtained, with the signal becoming weaker with each subsequent echo, as shown in Figure 2. Thus, the signal-noise ratio is a dominant factor in choosing the number of multiple echoes used for imaging. Since no one combination of TE and TR provides optimal viewing for all tissue types, this technique is used to provide images with a range of T1 and T2 weighting (multiple TE values).

Multislice imaging techniques have been developed to decrease patient examination time. In the standard spin-echo technique, TE is much shorter than TR—that is, 15 to 100 ms compared with 0.5 to 5 seconds—where a long TR is required to permit T1 relaxation of the sample slice before initiating the next imaging sequence. During this waiting period, adjacent slices of tissue can be imaged, as shown in Figure 3. Thus, the interleaving technique of multislice imaging permits acquisition of images from several slices during the time otherwise required to image only one slice. The number of slices constituting a multislice imaging procedure depends on the value of TR used.

The time saved can be illustrated by the equation for the imaging time, T, for a single slice:

$$T = TR \times n \times N$$

Here n is the number of imaging sequence acquisitions required per projection—that is, the number of averages plus one—and N is the number of measured projections—that is, the image matrix size. Thus, a single 256 × 256 slice with TR equaling two seconds and one average slice (two acquisitions) would take 17 minutes to acquire. Multislice techniques can provide as many as 20 such images in that amount of time. Producing multislice, multiecho images reduces to 12 the number of slices obtained for a four-echo sequence using the values above. Additional time savings can be achieved by improving the signal-noise ratio so that the number of imaging sequences, n, required can be reduced. Techniques being developed that use radio-frequency pulses to force T1 relaxation and thus reduce TR will also reduce scan times.

The multislice imaging technique, although simple in concept, introduces a variety of practical difficulties. Ideally, a

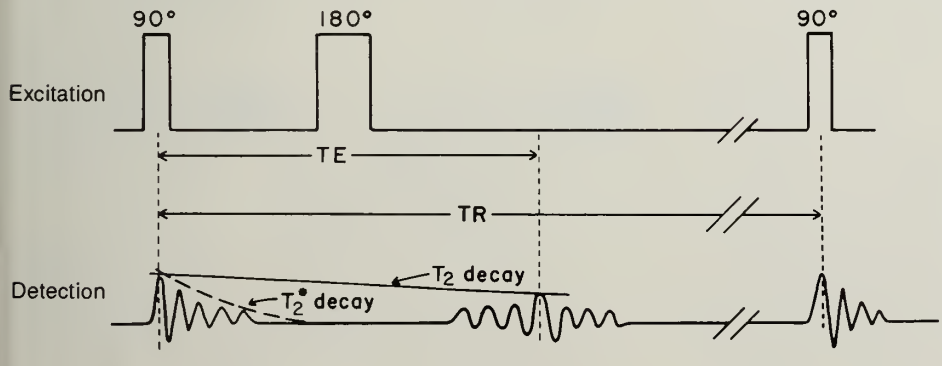

Figure 1.—Radio-frequency pulsing scheme and signals detected from a spin-echo pulse sequence. T2 = spin-spin relaxation time, T2* = spin-spin relaxation time and relaxation caused by nonuniformities in static magnetic field, TE = echo time, TR = repetition time

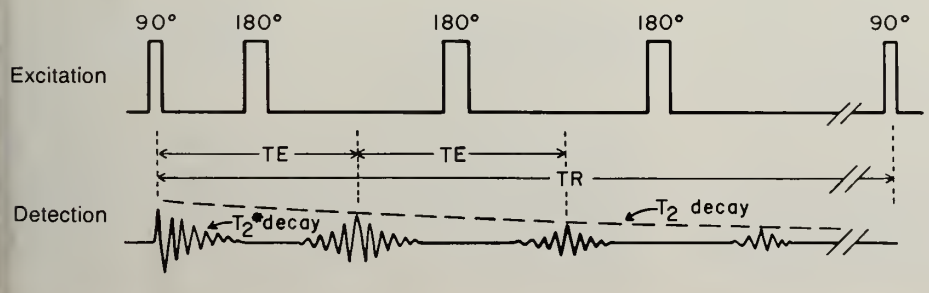

Figure 2.—Radio-frequency pulsing scheme and signals detected from a multiecho spin-echo pulse sequence. The symbols are as given in Figure 1.

sequence of adjacent images through the tissue volume of interest is desired, with no gaps of unimaged tissue and no overlap between slices. This objective is difficult to achieve, however, because the gaussian distribution of frequencies in the radio-frequency pulse causes excitation of tissue on either side of the desired slice (Figure 4-A). To avoid problems caused by the poorly defined borders of the tissue slices, multislice techniques traditionally provide images separated by gaps of unimaged tissue, with the gaps ranging from 3 to 10 mm.

Techniques have been devised to minimize the gaps between adjacent tissue slices. In one technique, an optimization approach is used to order the sequence of excited slices.[11] Another approach relies on two multislice acquisitions, with the second designed to produce images in the tissue regions constituting the gaps in the first acquisition. With a third technique, the radio-frequency pulse is tailored to provide a square, rather than gaussian, frequency profile, as shown in Figure 4-B. In this case, the radio-frequency pulse, $1f(t)$, is modulated by a sinc function, sinx/x, to give the radio-frequency pulse envelop shown in Figure 4-B. The result is a square frequency profile, $f(w)$, to define the slice. This technique requires rapid switching of the gradient fields making it more difficult to use at high field strengths.

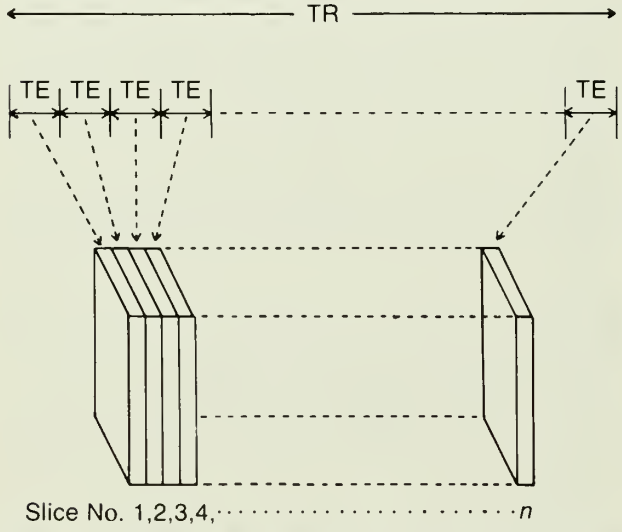

Figure 3.—Multislice imaging technique. The echo time (TE) span includes time to excite nuclei and record echo(es). TR = repetition time, n = number of imaging sequences

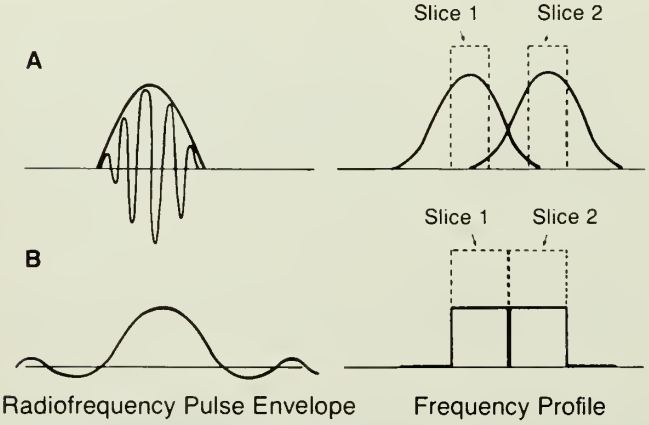

Figure 4.—Slice selection techniques: **A**, a typical gaussian radio-frequency pulse produces slices with overlap or gaps, or both. **B**, A sinc radio-frequency pulse produces slices with no overlap or gaps.

Volume imaging methods require considerable time and generate extensive data; hence, they are not used routinely.[12] Volume imaging techniques have one advantage, however, in that they do not produce slice overlap and gap problems as the entire volume of tissue is sampled simultaneously. Hence, these techniques have been used to provide thin, adjacent images, such as 0.9 mm slices with no gap, of small anatomic regions such as the pituitary[13] and heart.[14]

Conventional multislice spin-echo techniques have been modified to provide information about specific aspects of tissue pathology. Most hydrogen in tissue is present in water or in the long carbon chains of fat triglycerides. In fat, the hydrogen nuclei have a different chemical environment from that in water; consequently, the local magnetic fields are different and the Larmor frequency for hydrogen in water is shifted slightly from the frequency for hydrogen in fat. This chemically induced shift (termed a "chemical shift") is present as an artifact in conventional high-field images.[15] A chemical shift of 3.5 ppm for the hydrogen nuclei of fat and water is shown in Figure 5-A, where the units of chemical shift are stated as parts per million of the Larmor frequency of hydrogen in water. When stated in these units, the chemical shift is independent of field strength and is related to the actual shift in frequency by the expression

$$\Delta W = \delta \times W_L$$

where δ is the chemical shift (ppm) and W_L is the reference Larmor frequency. At 0.35 tesla ($W_L = 15$ MHz), the water and fat peaks are shifted by 53 Hz, whereas at 2 tesla ($W_L =$ 84 MHz), the same peaks are separated by 294 Hz. It is this

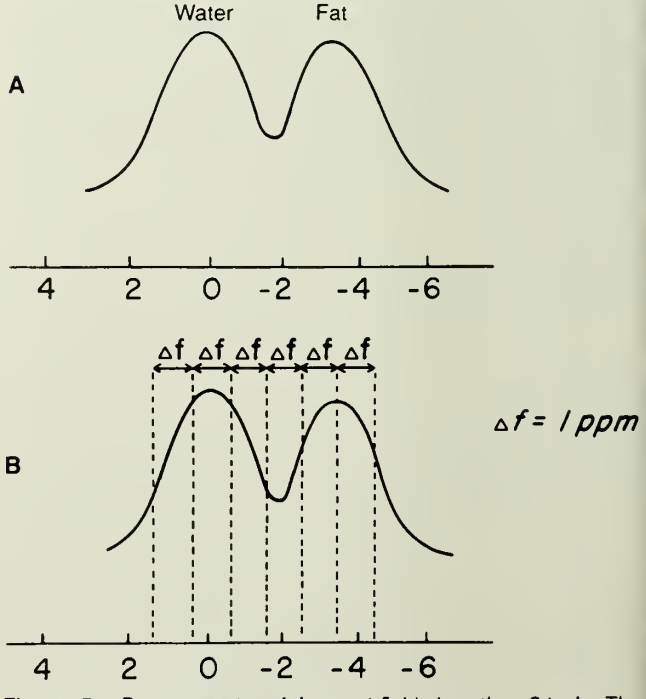

Figure 5.—Proton spectra of tissue at fields less than 2 tesla. The horizontal axis represents a chemical shift with respect to the water peak in units of parts per million of the Larmor frequency of hydrogen in water (see text). **A**, Proton spectra and **B**, slices obtained with a resolution of 1 ppm by the 3-dimensional Fourier transform technique of Pykett and Rosen.[16]

larger shift at higher frequencies that produces an artifact when imaging at higher field strengths.

Chemical shift imaging techniques, employing a modified form of the conventional spin-echo sequence, have been used to obtain separate images of water and fat distributions in tissue at field strengths as low as 0.15 tesla.[17,18] Two imaging sequences are required with this approach to obtain four sets of images: fat plus water, fat and water difference, fat only and water only. Images are obtainable within the same time and resolution constraints as conventional spin-echo techniques. With higher field systems, a three-dimensional Fourier transform technique can be used to obtain images of the signal intensities of the hydrogen spectral peaks at a separation of 0.1 ppm. For fat and water, separate images can be obtained at several positions in the hydrogen spectrum as shown in Figure 5-B. If desired, peaks in the water or fat range can be summed to yield a total water or total fat image.[16] A third technique involves obtaining a water image by saturating the fat resonance before conducting a traditional spin-echo two-dimensional Fourier transform imaging sequence. To illustrate, the fat resonance can be irradiated with a 90° pulse before beginning the normal imaging sequence by a radio-frequency pulse at the resonant frequency of fat. When combined with the first 90° pulse of a traditional spin-echo imaging sequence, the fat resonance will have undergone a 180° flip, making its signal invisible to the MR receiver coil.

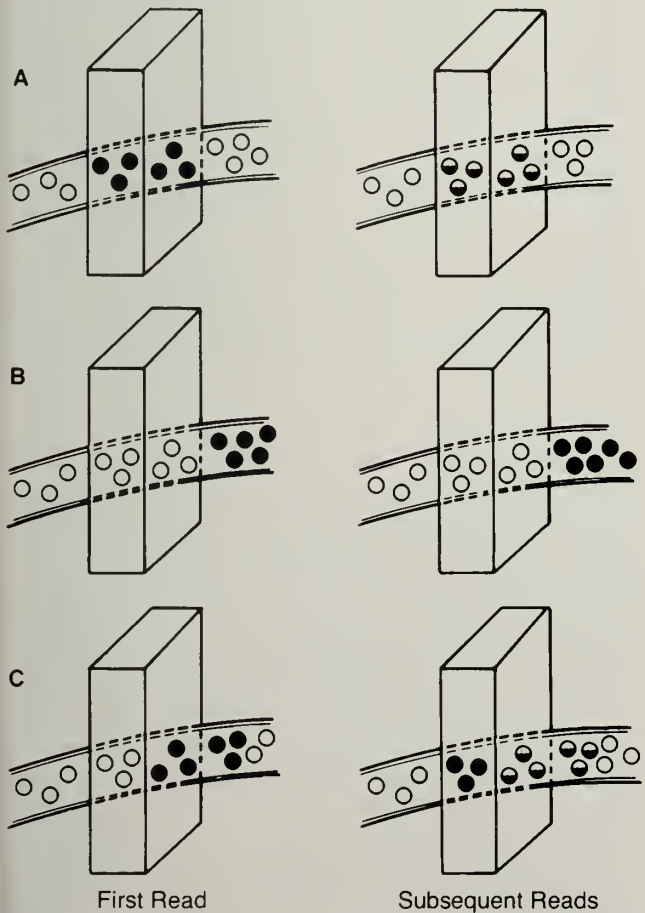

Figure 6.—This diagram shows the effect of blood flow on the magnetic resonance image intensity: **A**, Stationary blood, **B**, fast-flowing blood and **C**, slow-flowing blood.

Conversely, a fat image can be obtained by first saturating the water peak.[19] At present, chemical shift imaging is an experimental technique; images have been useful, however, in showing fatty infiltration of the liver.[20]

Another anomaly of conventional imaging is the influence of blood flow on signal intensity in vascular structures.[21] As an illustration, stationary blood would be expected to behave like tissue in terms of magnetic resonance imaging. In a spin-echo sequence, the initial radio-frequency pulse produces a maximal signal, with negligible relaxation occurring between the 90° pulse and the measurement of the radio-frequency signal. But, if a TR is chosen so that the nuclei remain partially saturated—that is, not completely relaxed—for all subsequent 90° pulses, the resulting signal intensity is diminished, as diagrammed in Figure 6-A.

For fast-moving blood (10 cm per second or faster),[21] protons initially excited by the radio-frequency pulse move out of the image plane before the signal is measured, as shown in Figure 6-B. Blood moving into the image plane has not been exposed to a radio-frequency pulse and hence yields no signal. In the image, fast-moving blood is shown as a dark, signal-less region.

With slow-moving blood, these two events are combined to provide a signal greater than that from either stationary or fast-moving blood. During the repetition time, the partially saturated blood remaining from the previous sequence is replaced in part by blood flowing into the imaging plane. The subsequent 90° radio-frequency pulse elicits a stronger signal from this new blood (Figure 6-C) than from the remaining partially saturated blood and the total signal is enhanced over that of stationary blood. This effect is referred to as "paradoxical enhancement" and yields a bright area in regions of the image representing slow-moving blood. Slow flow can also be distinguished by a distinct rephasing effect on even echoes of a multiecho imaging sequence.[22] Because of these flow effects, information about flow velocities can be elicited by appropriate manipulation of the image sequence variables TE and TR.[23,24] Recent studies suggest that flow measurements from imaging techniques may depend also on other aspects of the measuring technique, such as the reconstruction algorithm.[25]

Image Quality

As in any imaging modality, image quality is a subjective characteristic; nevertheless, certain image variables can be measured as an indication of image quality. These variables include the ratio of signal to noise, the ratio of contrast to noise, spatial resolution, the presence (or absence) of artifacts and the accuracy of T1 and T2 values determined from the image. To date, quantifiable standards have not been developed for an overall evaluation of the quality of magnetic resonance images; hence, vendors tend to emphasize the image variables at which they excel.

For an MR image, the signal-noise ratio is commonly described by the equation

$$S\text{-}N = (I_T - I_B)/\sigma_B$$

where I_T and I_B are the signal intensities of the tissue of interest and the image background, and σ_B is the standard deviation of the background signal. The signal-noise ratio depends strongly on the pulse sequence and pulsing times used for

imaging. For example, it is obvious from Figure 2 that the signal I_T from the tissue depends on which echoes are used to form the image and that the background signal is constant. Values of signal-noise ratio ranging from 10 to 100 are frequently quoted[26,27]; these values are obtained at different pulse sequences and pulsing times, however, and it is difficult to compare the signal-noise specifications from one vendor to another. Signal-noise values are often quoted in association with the field strength issue discussed below but these quotations frequently shed little light on the issue.

The contrast-to-noise ratio is similar to that of signal to noise, except that it is used to measure the difference in signal, and thus the visibility, of two different tissues of interest, such as gray and white matter or tumor and normal tissue. The contrast-noise ratio is described by the expression[5]

$$C\text{-}N = (I_{Ta} - I_{Tb})/(I_0\sigma_B)$$

where I_{Ta} and I_{Tb} are the signal intensities of the two tissues of interest. I_0 is the maximal signal measurable for the two tissues—that is, the signal obtained after a single 90° pulse is applied following complete longitudinal relaxation of the tissue—and σ_B is the standard deviation of the background. If the spin densities of the two tissues are equal, they should have the same value for I_0 irrespective of the imaging regimen used; I_{Ta} and I_{Tb} are not independent of the selected imaging regimen, however. Hence, the maximal contrast-noise ratio is often used to predict the optimal pulse sequence for imaging specific tissues.[6]

Both the signal-noise and contrast-noise ratios affect the spatial resolution of the magnetic resonance image. Values for the spatial resolution are often quoted, inappropriately, as the predicted picture element (pixel) size of the image. That is, for an anatomic region of 30 cm by 30 cm, a 128×128 image will provide a pixel size of 2.3 mm; for a 256×256 image of the same object, the pixel size will be 1.15 mm.

An increase in matrix size to decrease pixel size requires a dramatic increase in imaging time, as N increases in the expression for imaging time presented earlier. Slice thickness can be reduced in an effort to decrease partial volume effects and to improve resolution. With reduced slice thickness, however, more slices are needed to encompass a given volume of tissue, and the imaging time increases. As is apparent from these examples, there is almost always a trade-off between spatial resolution and imaging time.

In actuality, the signal-noise ratio provides a practical limit to the effective spatial resolution. The borders of a volume element of tissue (voxel) are defined by the pixel size and the slice thickness. As the voxel size is reduced, there are fewer resonating nuclei present in the voxel, causing a reduction in the measured signal and a decrease in signal-noise ratio. This decrease places a practical limit on the spatial resolution obtainable with an MR imaging unit.

Motion artifacts occur in MR imaging principally because of the length of time required to obtain a set of MR images. These artifacts are especially apparent in images of the thorax and upper abdomen.

Cardiac studies with MR imaging can be gated to the R wave and the electrocardiogram to decrease motion artifacts; detailed images of as many as ten sections obtained at one to five different times during the cardiac cycle have been published.[14] One disadvantage of cardiac gating is that the TR interval depends on the pulse rate. Consequently, the TR cannot be easily manipulated; in fact, TR is never constant as the pulse rate is often variable. This variability interferes with computing of the tissue relaxation characteristics, T1 and T2.

Gated cardiac images can be obtained with either multislice or volume imaging techniques. Unless a special sequencing procedure is used, however, multislice techniques yield images of sequential slices at different times in the cardiac cycle, because the slices cannot be taken simultaneously. Volume imaging techniques require longer times for acquiring data, but they can provide slices produced at the same time in the cardiac cycle. Presently, cardiac images are produced in the standard orthogonal planes. Techniques are being developed, however, to produce images in oblique planes that correlate more closely with conventional radiography.[28-30]

Images of the upper abdomen often contain artifacts caused by respiratory motion. The respiratory cycle is not constant in either depth or length, and gating of respiratory motion is difficult. Gross motion artifacts have been removed by respiratory gating, but at the cost of a 1.5 to 2 times increase in imaging time, depending on the characteristics of the respiratory cycle.[31]

Motion artifacts can also be eliminated by the use of the echo planar imaging technique.[32] This technique uses an oscillating gradient field to localize the signal in the traditional phase encoding plane of a normal two-dimensional Fourier transform imaging method.[5] In contrast to this traditional imaging method, a separate data collection sequence for each of N pixels in the phase encoding direction is not required. Scan times are reduced to 10 to 100 ms per slice because all of the image data for one planar slice are obtained from one pulsing sequence. To date, echo planar imaging has been used primarily for the thorax, where 32 slices with 16 images per slice at 16 phases of the cardiac cycle have been produced (512 images total).[33] A typical examination is completed in four to eight minutes, depending on a patient's cardiac period. Because of signal constraints, these images have only 32×32 pixel resolution (6 mm) and a slice thickness of 8 mm. To date, echo planar imaging has been done only at low fields (0.1 tesla); the technique requires the rapid switching of gradient magnetic fields, and it is uncertain whether it will be feasible at higher field strengths. To overcome this difficulty, hybrid techniques involving a combination of two-dimensional Fourier transform and echo planar imaging are being investigated.

Another measure of image quality is the accuracy of T1 and T2 values calculated from the image. In 1971, Damadian[34] suggested that normal and malignant tissue may be distinguishable on the basis of differences in their T1 values. Subsequent conflicting reports have appeared concerning the value of T1 and T2 as tissue-specific indicators.[35-37] Much of the conflict has been attributed to inaccuracies in the T1 and T2 values extracted from images. These inaccuracies arise from the numerous errors inherent in the measuring technique.[38,39] These include high noise levels, effects of flow and motion, partial volume effects, slice overlap and nonuniform excitation of slices. Recent reports, however, have shown accuracies of 96% to 98% in measured T1 and T2 values for a few types of tissues and test solutions.[40,41]

Contrast Agents

The contrast in a magnetic resonance image is a reflection primarily of differences in T1 and T2 relaxation times among

various tissues. By using in vivo contrast agents to selectively alter the relaxation times, image contrast often can be improved. Contrast agents currently under investigation are principally paramagnetic materials. These substances have large magnetic moments resulting from the presence of unpaired electrons in the atomic structure. The presence of a paramagnetic substance alters the magnetic field in the immediate vicinity of the substance. This alteration facilitates relaxation and shortens T1 and T2 relaxation times.[42,43]

Paramagnetic agents investigated to date have primarily been complexes and salts of the transition metals and rare earth elements, including manganese, iron, cobalt, nickel. copper, chromium and gadolinium. Intravenous injections of manganese chloride have altered the T1 values of abdominal organs.[44] Recent studies have contradicted earlier reports of the high toxicity of this material.[45] Manganese has also been complexed to a monoclonal antibody in an attempt to provide better delineation of myocardial infarction.[46]

Weak Geritol solutions containing ferrous ammonium citrate can be used as a nonhazardous orally administered contrast agent to enhance the image of the gastrointestinal tract.[47] Recently an iron complex, iron (III) ethylene *bis*-(2-hydroxyphenylglycine) or Fe(EHPG), has been shown to enhance the imaging of normal liver parenchyma without adverse effects in rats.[48]

One of the more promising contrast agents is a complex of gadolinium (Gd) with diethylenetriaminepentaacetic acid (DTPA).[49,50] Administered intravenously, Gd-DTPA is used as an indicator of organ perfusion[51] and has been compared in behavior with the iodinated contrast agents used in computed tomography (CT).[52] Gd-DTPA has been effective clinically in enhancing the images of brain tumors,[53] brain abscesses[54] and ischemic myocardial tissue.[55,56] Early studies have shown no toxicity of the agent[45] and it is currently undergoing phase III trials in humans in four institutions.

Nitrogen-stable free radicals are another class of contrast agents under investigation. Free radicals are paramagnetic because they possess an unpaired electron in the valence molecular orbital.[42,43] Nitrogen-stable free radicals have been shown to enhance the imaging of renal[57] and brain[58] tissues; toxicity studies are ongoing.

Radio-frequency Coils

Recent improvements in MR image quality are attributable in part to design improvements in radio-frequency coils. To illustrate, a saddle-shaped radio-frequency coil is placed inside a solenoidal magnet as shown in Figure 7. If an alternating current (AC) is transmitted through the coil, an alternating B_1 field is generated perpendicular to B_0, the static magnetic field, and the coil acts as a transmitter. Conversely, if an oscillating magnetic field produced by precessing nuclei in the plane perpendicular to B_0 is sensed by the coil, a current is generated in the coil and the coil acts as a receiver.

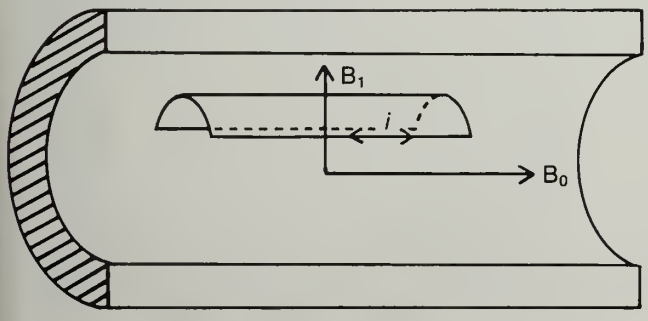

Figure 7.—A saddle-shaped radio-frequency coil inside a solenoid magnet. B_0 = the direction of the magnetic field of the solenoidal magnet, B_1 = the direction of the magnetic field produced by current flow, *i*, in the radio-frequency coil.

A radio-frequency coil is often represented as a series LRC circuit, where L is the circuit inductance, R is the resistance and C the capacitance.[59] The coil is most sensitive to the magnetic resonance signal when the AC frequency of the circuit, given by

$$f = (2\pi)^{-1}(LC)^{-1/2},$$

is tuned to the Larmor frequency. In this condition, the coil will provide the largest MR imaging signal in response to the precessing nuclei. When a body (a load) is placed in the coil, additional inductance and capacitance are encountered, thus altering the optimal receiving frequency of the coil from that of its unloaded state. Most MR imaging systems permit fine tuning of the coil frequency to obtain the maximum signal with the patient in place.

Any radio-frequency coil is sensitive to a range of frequencies, Δf, about the center Larmor frequency. This range of frequencies—the bandwidth—is described by the coil Q, where a high Q means a narrow bandwidth, as shown in Figure 8. A high Q coil is preferred because it limits the amount of noise detected by the coil. When a body is placed in the coil, Q is decreased significantly below its unloaded value, with the decrease dependent on the tissue volume encompassed by the coil.

Coil geometries are determined by the desire to provide homogeneous radio-frequency fields for irradiating and measuring samples and to maximize the amount of tissue located in the radio-frequency field. This latter factor is referred to as the filling factor of the coil, and a higher filling factor provides a stronger signal. Typical coil arrangements include solenoid coils in permanent magnet systems and saddle-shaped coils in resistive and superconducting magnet systems. At high fields (greater than 1 tesla), the coil geometries have to be modified extensively because the coil length becomes comparable with the radio-frequency wavelength and phase shift artifacts occur.[60]

Finally, coil optimization includes eliminating other

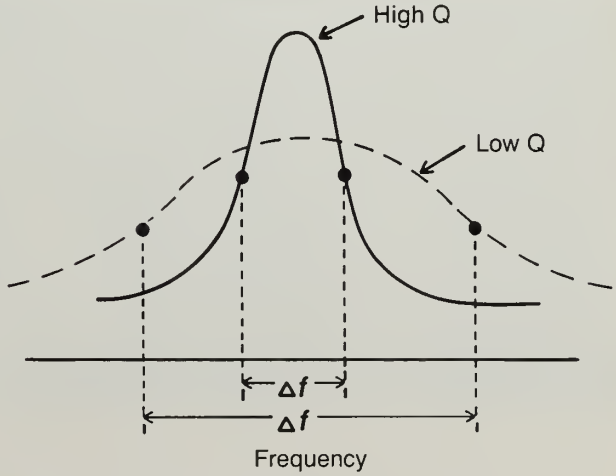

Figure 8.—Dependence of bandwidth, Δf, of coil on value of coil Q.

sources of noise such as mismatching of coil and amplifier impedances and other electronic signal losses.

A significant improvement in coil operation has resulted from decoupling of the transmitter and receiver coils. In an MR imaging unit, the transmitter typically generates high-powered pulses (10 kW), while the receiver coil must be sensitive to microvolt (μV) return signals. By creating two separate coils and positioning them orthogonally to each other, cross talk between the coils can be eliminated and the coils can be individually optimized. Currently, manufacturers are investigating the use of quadrature transmitting and receiving coils as another means of improving sensitivity.[61] In a quadrature coil system, two coils are located orthogonally to each other. Signals in the two coils are phase shifted with respect to each other to reduce noise and the use of two coils increases the signal obtained from the tissue sample.

Perhaps the most exciting coil development has been the use of surface coils to produce high-resolution images of superficial structures such as the spine, orbits, neck and breast.[62-64] Surface coils are typically circular or elliptical in shape and contoured to the body region to be imaged. In this manner the filling factor is increased and noise from other regions of the body is decreased, yielding a higher signal-noise ratio, finer resolution and thinner slices. Penetration of the radio-frequency signal is limited to a depth equal to the coil's radius. In addition, the smaller coils have less homogeneous radio-frequency fields and tissues are not uniformly excited, resulting in nonuniformity of signal intensity in images.

Some nonuniformity can be avoided by decoupling the transmitting and receiving coils. Decoupling typically is accomplished by using the standard head or body coil as the transmitter and the surface coil as the receiver coil. Usually the head or body coil is located farther from the imaged region and irradiates the entire tissue volume inside the coil; hence, more power is deposited in the patient with the decoupling technique. (A surface coil for the spine is shown in Figure 9. Also shown is the difference in resolution and uniformity for a standard body coil compared with the surface coil.)

Siting

Siting considerations depend on both the geometry and the field strength of the magnet. Because of their solenoidal geometry, superconducting and resistive magnets exhibit fringe magnetic fields. The extent of these three-dimensional stray fields depends on the field strength of the magnet. A typical 0.5-tesla magnet has a stray field strength of 5 gauss (G)—1 gauss = 0.0001 tesla—along the magnet axis at a distance of 8 m from the magnet center. This distance increases to 12 m for a 1.5-tesla magnet. Because of these stray magnetic fields, it was originally thought that MR imaging units (especially high field strength units) had to be sited in separate, remote buildings. Subsequently, it has been learned that even high field strength units can be housed in existing facilities by the use of steel enclosures and improved engineering design.[65,66] MR imaging units using permanent magnets do not produce significant fringe magnetic fields.

The interaction between an MR imaging unit and its environment is twofold: the stray magnetic field exerts an influence on the surrounding environment and personnel, and ferromagnetic materials in the environment influence the homogeneity of the magnetic field within the magnet bore. Site planning guides of different vendors vary considerably in their precautions against using electronic equipment around MR imaging units. Magnetic storage media (computer tapes and credit cards) and equipment that relies on electron beams (video monitors and cathode ray tubes) and photomultiplier tubes (CT units and scintillation cameras) can be affected. Little data are available on the intensity thresholds for the effects of magnetic fields on the operation of electronic equipment; in all likelihood, values would vary depending on the design and inherent shielding of the instrument. In general, vendor guidelines are conservative with respect to instrument function, erasing of stored data and so forth; experience to date is inadequate to address effects occurring over a longer term.

Guidelines for the location of ferromagnetic materials near the magnet are also provided in vendor guides. Large masses of stationary ferromagnetic materials can normally be compensated by "shimming" during installation of the MR imaging unit. Transient masses of ferromagnetic materials of any size should not be allowed near the MR imaging unit because they distort the magnetic field; they also could be hazardous if pulled towards the magnet. Large transient ferromagnetic objects, such as automobiles, elevators and trans-

Figure 9.—Left, An elliptical surface coil used for spine imaging. **Middle,** A spine image obtained with a standard body coil. **Right,** A cervical spine image obtained with a surface coil. Note the higher image detail in the region of interest but lower image uniformity. (Photographs courtesy of R. Edward Hendrick, PhD, Department of Radiology, University of Colorado Health Sciences Center.)

port carts, should be kept outside of the 1-gauss field lines to avoid distortion of the magnetic field in the imaging unit.

With regard to steel enclosures for MR imaging units, assorted shielding configurations have been used, including a cylindrical barrel-shaped dome,[67] parallel plates and a rectangular box.[68] One advantage of the box design is that it can also provide radio-frequency shielding. Self-shielded magnets have also been designed[69]; usually these require some additional room shielding to reduce stray fields to levels comparable with those in a shielded facility.

Other major siting considerations include radio-frequency shielding,[70] access route for a superconducting magnet, weight distribution for a permanent magnet and cryogen venting. Most vendors provide detailed guidelines to address these issues. Of course, if permanent siting of an MR imaging system is a problem, mobile units of nearly all available field strengths and magnet types can be purchased.

Safety

Potential bioeffects from MR imaging have been extensively reviewed.[3] Although past studies indicate that there are no harmful bioeffects associated with MR imaging, investigations continue on the premise that negative results do not rule out all possible risks.

In recent studies there was no evidence of damage or genetic aberration of cells at fields up to 2.7 tesla and exposure times up to 17 hours.[71,72] An epidemiologic study of 792 workers at national laboratories exposed to static magnetic fields of 0.5 millitesla to 2 tesla showed no increased incidence in 19 disease classifications.[73]

No change in pineal function was noted during MR imaging of four subjects.[74] The only documented bioeffect was the induction of visual sensations by changing magnetic fields of 1.3 tesla per second at a rate of 15 per second. This effect has been attributed to a torque that alters the shape of retinal rods.[75] No evidence has been reported that this effect is either deleterious or permanent.

Guidelines of the Center for Devices and Radiological Health (formerly the Bureau of Radiological Health) remain as established in 1982.[76] Levels considered safe include static magnetic fields below 2 tesla; time varying fields less than 3 tesla per second and radio-frequency exposures causing specific power absorption rates less than 2 W per kg over 1 gram of tissue and 0.4 W per kg over the entire body. The Food and Drug Administration (FDA) has granted approval to nine commercial systems that adhere to these guidelines. In addition, conditional FDA approval has been awarded to three systems (Table 1). Approval is limited to specific imaging systems and techniques. Any changes in these systems such as increasing field strength or changing imaging protocols require further approval from the FDA.

Although no tissue damage has been shown from MR imaging, there are specific contraindications for an MR imaging examination. The presence of magnetic fields of 17 G or greater has been shown to switch cardiac pacemakers to asynchronous (nondemand mode) operation.[77] These and other electronic implants are susceptible to malfunction due to voltages induced by changing magnetic fields. In addition, radio-frequency pulses of sufficient amplitude and pulse rate can potentially mimic electrical activity of the heart and interfere with the proper operation of cardiac devices. Hence, implant

TABLE 1.—*Magnetic Resonance Imaging Units Approved by the Food and Drug Administration (FDA)*

Vendor	*Field Strength, telsa*
Diasonics Inc	0.35
Fonar	0.3
General Electric Co	0.5, 1.0, 1.5
Picker International Inc—head, neck	0.5
Picker International Inc—body	(0.5)*
Siemens Medical Systems Inc	0.35, 0.5, (1.0)*, (1.5)*
Technicare Corp	0.5

*Recommended for FDA and approved by the FDA Advisory Board.

patients should not be imaged; in fact, they should be excluded from areas where the magnetic field exceeds 5 G. Other contraindications at present include patients who are subject to seizures, claustrophobia, cardiac arrest or who are unconscious or morbidly ill.

Ferromagnetic materials are attracted by magnetic fields and experience a torque causing them to line up with the field. Persons containing such devices should not be imaged by magnetic resonance. In a study of metallic surgical and dental implants, 16 of 21 vascular clips and one shunt connector were found to be affected by MR imaging magnetic fields.[78] Forces on five clips were considered sufficient to dislodge or displace the clip, possibly causing hemorrhage or cerebral injury. Unaffected metallic devices were nonferromagnetic and made from high nickel (10% to 14%) stainless steel, alloys, tantalum or titanium.

At many sites patients with a surgical history are required to provide appropriate medical records or obtain an x-ray examination to document the presence or absence of surgical clips. Only when the radiologist is confident that implants are nonferromagnetic should a person be imaged.

Eye makeup also contains ferromagnetic material that can cause eye irritation during or after imaging. Patients should remove heavy eye makeup before an examination.

Another biological concern of MR imaging arises from its potential to heat metallic implants such as prostheses, surgical clips and intrauterine devices. The heating is caused by electrical currents induced by changing magnetic and radio-frequency fields. Heating effects have not been seen except in one case of two hip prostheses subjected to MR imaging regimens in vitro in a conducting saline solution.[79] In general, patients with metallic implants can be imaged successfully.[80]

Ferromagnetic objects such as pens, scissors, tools and gurneys are attracted to the magnet and should be excluded from the room. The potential for patient injury from these flying objects is probably the chief biohazard of MR imaging. Metal detectors sensitive enough to pick up such objects will also detect nonhazardous objects on MR personnel (belt buckles, jewelry and the like) and thus are relatively ineffective as a screening technique. Usually warning signs and personnel education are sufficient to keep ferromagnetic objects from the examination room.

Wheelchairs and gurneys needed for nonambulatory patients should be nonferromagnetic, such as aluminum. Crash carts are typically ferromagnetic and contain equipment (respirators, defibrillation and so forth) that may not function properly in an intense magnetic field. If emergency resuscitation is required, a typical crash cart should not be brought into

the magnet room. Instead, a core area should be available outside the scan room and a strong nonferromagnetic gurney[81] or removable MR imaging table should be available for rapid transport of the patient to the core area.

MR Field Strength

The optimum field strength for MR imaging is probably the most hotly contested issue among researchers. Resolving this issue is complicated by the marketing strategies of major equipment manufacturers[82] and by the uncertainty of selected clinical applications of magnetic resonance. Questions related to the field strength issue involve image quality (signal-noise ratio, resolution, slice thickness), imaging times, radio-frequency power deposition, spectroscopic applications, cost and siting.

Fundamental to the field strength debate is the fact that the magnetic resonance signal increases with magnetic field strength. As the field strength increases, the energy difference increases between the nuclei aligned with and against the field. Because more energy is required to align against a more intense field, a greater number of nuclei adopt the lower energy state of alignment with the field. This alignment process yields an increase in signal strength because the signal depends on the population difference between the two energy states. Noise also increases with a higher field, but theoretically not so rapidly as the signal. At low fields, noise results mainly from radio-frequency coils and assorted electronics; at higher fields it emanates chiefly from the object being imaged. As a result, the signal-noise ratio can be shown theoretically to increase with magnetic field strength. A higher signal-noise ratio should yield an improved image. In general, researchers agree with this basic tenet, but they argue over the rate of increase of the signal-noise ratio with field strength and whether the improvement in image quality is enough to justify the cost of a higher field magnet.[26,83]

By the same theoretical arguments, proponents of high field systems predict that the contrast-to-noise ratio increases with field strength. The contrast-to-noise ratio is thought to be a very important variable because contrast determines the visibility of tissue structure. Differences in T1 values among tissues, however, decrease with increasing field strength,[84] and this decrease results in a decrease in the contrast-noise ratio.[85,86] High-field proponents counter that T2, which is independent of field strength, has a greater influence on contrast than does T1; hence, the contrast-noise ratio does increase with field strength.[87,88]

Practical advantages of an increased signal-noise or contrast-noise ratio should include improved image quality and thinner slices. A certain level of signal is required from any tissue if an image is to be produced. If the signal can be increased, then one should be able to subdivide the tissue volume and still obtain sufficient signal from each of the small volumes to produce a higher resolution or thinner section image. Some workers say that the signal increase can be accomplished by using higher field systems. Others counter that the image is degraded at higher fields, by the chemical shift effects discussed previously. Two methods for improving resolution are shown in Figure 10. In the first method (Figure 10-A), the resolution element, ΔZ, is decreased by narrowing the bandwidth, Δf, of the radio-frequency signal while the gradient is kept constant. At higher field strengths, this method is not feasible as the fat and water proton peaks are separated too widely. Instead, a technique of increasing the gradient strength is used (Figure 10-B). With this approach, a smaller region, ΔZ_A, can be imaged for the same bandwidth pulse. Noise levels also increase with increasing gradient strength, thereby setting a limit on the available improvement of signal-noise ratio. Proponents of high field systems claim that chemical shift is not a problem in the head, but concede that it may be troublesome in body imaging.[82]

An increase in the signal-noise ratio can also reduce patient examination times by decreasing n, the number of signal averages required to produce sufficient signal-noise ratio in an image. As shown previously, the examination time increases linearly with n, as well as with TR and N. Proponents of low fields claim that a larger TR is needed at high fields because its choice depends on the T1 values of tissues, and T1 has been shown to increase with field strength.[89] In addition, if low field images can be produced at values of $n = 1$, then any possible high field advantage is negated. In fact, imaging will take more time because of increases in TR.

Another influence on imaging time is the increase in radio-frequency power absorption at higher field strength. Power levels can even exceed the guidelines of the Center for Devices and Radiological Health when rapid pulsing schemes required for efficient multislice imaging are used. Power levels can be reduced by decreasing the number of sections

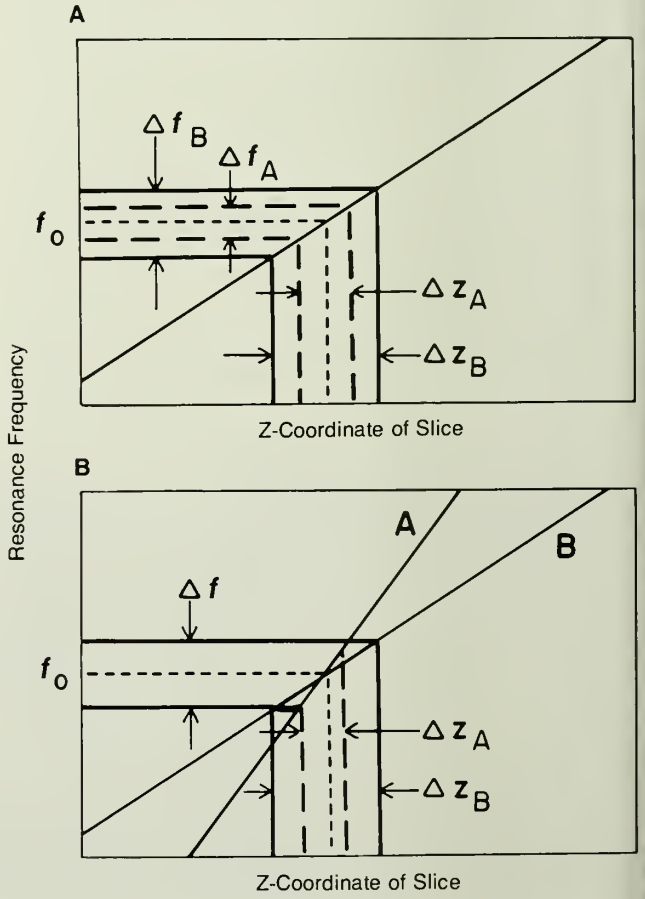

Figure 10.—Techniques for reducing the slice thickness. **A,** The bandwidth Δf_A is narrower than Δf_B, producing a thinner slice thickness ΔZ_A. **B,** The gradient strength A is steeper than B, producing a thinner slice thickness ΔZ_A.

taken simultaneously, but this approach increases examination time. Proponents of high field systems argue that the power deposition guidelines are too low and will eventually be raised.[82]

For spectroscopic studies of nuclei other than hydrogen, there is no question but that high field systems are required. Phosphorus,[90] sodium[91] and fluorine[92] images have been produced at fields of 1.5 to 2 tesla; they yield rather poor spatial resolution images, however, and require long imaging times. Some researchers are investigating fields from 4 to 8 tesla for spectroscopic imaging.

From a purchaser's standpoint, system cost and siting must also be considered as two factors associated with field strength. A higher field system (1.5 to 2 tesla) costs about $1 million more than does a low field (0.6 tesla or less) unit. Although high field units can be sited in existing facilities, the shielded rooms average $500,000. Without question, a potential purchaser of an MR imaging unit needs to be familiar with the many issues associated with controversy over high- and low-field MR imaging units and how these issues relate to the specific intended use of the MR imaging system.

The many technical advances discussed here have yielded appreciable improvement in image quality and clinical utility of MR imaging over the past few years. Many of these improvements are summarized elsewhere in this issue.* This imaging procedure is still in its infancy and there is no reason to believe that the current rate of advancement will not be maintained for several years.

*See "Clinical Applications of Magnetic Resonance Imaging—Current Status" by D. Cammoun, MD; W. R. Hendee, PhD, and K. A. Davis, MD, pp 793-803.

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Clinical Applications of Magnetic Resonance Imaging—Current Status

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Magnetic resonance imaging has far-reaching real and possible clinical applications. Its usefulness has been best explored and realized in the central nervous system, especially the posterior fossa and brain stem, where most abnormalities are better identified than with computed tomography. Its lack of ionizing radiation and extreme sensitivity to normal and abnormal patterns of myelination make magnetic resonance imaging advantageous for diagnosing many neonatal and pediatric abnormalities. New, reliable cardiac gating techniques open the way for promising studies of cardiac anatomy and function. The ability to image directly in three orthogonal planes gives us new insight into staging and follow-up of pelvic tumors and other pelvic abnormalities. Exquisite soft tissue contrast, far above that attainable by other imaging modalities, has made possible the early diagnosis of traumatic ligamentous knee injury, avascular necrosis of the hip and diagnosis, treatment planning and follow-up of musculoskeletal neoplasms.

(Cammoun D, Hendee WR, Davis KA: Clinical applications of magnetic resonance imaging—Current status, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:793-803)

Magnetic resonance (MR) imaging has the potential to portray normal anatomy and to show abnormal conditions in many of the body's organ systems and anatomic regions. In this article we examine the current realization of this potential for several regions and organ systems, including the central nervous system (CNS), head, neck, mediastinum and chest, cardiovascular system, breast, abdomen, pelvis and musculoskeletal system.

Central Nervous System

Many studies have confirmed the ability of MR imaging to show abnormalities in the entire central nervous system, including the brain, the brain stem and the spinal cord. This ability has caused some imaging physicians to identify MR imaging as the preferred imaging modality for many CNS diseases. Although other specialists have been a bit more cautious, there is little question that MR imaging will be extremely valuable in diagnosing a wide spectrum of CNS disorders.

Posterior Fossa

Magnetic resonance imaging is an ideal tool to explore the posterior fossa. It provides exquisite contrast sensitivity and is not impeded by the thickness of the skull in this region (Figure 1). Sagittal views are particularly useful for posterior fossa studies.

Low-grade lesions in the posterior fossa, including brainstem tumors, are detected more reliably with MR imaging than with computed tomography (CT).[1-3] MR imaging is an accurate method for detecting masses in the cerebellopontine angle and is a noninvasive alternative to contrast-enhanced CT and air cisternography in diagnosing acoustic neuroma.[4] In part, these advantages are due to the absence of signal from the petrous bone.

Brain Tumors

Magnetic resonance imaging appears to be the preferred modality for investigating many brain tumors, primarily because many—but not all—tumors have increased spin-lattice (T1) and spin-spin (T2) relaxation times. Small meningiomas can be missed because of their variable T2 relaxation time; the use of gadolinium (Gd)-diethylenetriaminepentaacetic acid (DTPA) as a contrast agent for MR imaging seems to improve the detection of meningiomas.[5] Compared with adjacent normal brain tissue, meningiomas are often hypointense—that is, dark when a spin-echo pulse sequence is used with a short repetition time. At other times a meningioma has a characteristic thin hypointense rim that delineates the tumor.[5] Separation of tumor from surrounding edema has been possible in several instances.[3] However, MR imaging produces results superior to those of CT only if a clinician knows which pulse sequence to use and how to select the pulse vari-

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
Gd-DTPA = gadolinium-diethylenetriaminepentaacetic acid
MR = magnetic resonance
T1 = spin-lattice relaxation time
T2 = spin-spin relaxation time

ables within that sequence. Obviously, this statement is true not only for the detection of brain tumors but for lesions in general.

In patients with neurofibromatosis, MR imaging is useful in delineating lesions such as optic gliomas, bilateral acoustic neuromas, meningiomas, infiltrating gliomas and hamartomas. It may also prove useful in determining which neurofibromas have progressed to neurofibrosarcoma.[6]

Inflammatory Disease

Multiple sclerosis is the most disabling neurologic disease to strike young adults.[7] Early diagnosis of multiple sclerosis is difficult to establish, and the disease is often unrecognizable at an early stage on CT images. MR imaging is a much more sensitive technique than CT for detecting chronic plaques of multiple sclerosis, even when the standard examination is a delayed double-dose-enhanced CT scan.[7] In the acute phase, MR imaging and CT appear to have about equal sensitivity.

Multiple sclerosis lesions have prolonged T1 and T2 relaxation times and are observed in periventricular deep white matter as well as in the cerebellum, brain stem and spinal cord. Multiple sclerosis plaques can also be seen at the junction of grey and white matter and in grey matter. If there is no clinical evidence of multiple sclerosis, these findings suggest additional differential diagnoses, such as multiple infarcts within the deep white matter, Binswanger's disease (subcortical atherosclerotic encephalopathy), vasculitis, early metastases without mass effect or edema, progressive multifocal leukoencephalopathy, encephalitis and normal aging. Sometimes large or confluent multiple sclerosis plaques resemble metastases with mass effect and edema.

Focal lesions have been found by MR imaging in eight patients with systemic lupus erythematosus and the recent onset of neuropsychiatric symptoms. Corresponding CT findings were visible in only two of seven of these patients.[8]

Trauma

Magnetic resonance imaging is very sensitive to parenchymal cerebral contusions and small subdural hematomas. Gandy and co-workers found MR imaging helpful when standard skull radiography and CT showed no evidence of these conditions.[9] Acute subarachnoid and intracerebral hemorrhage undergoes three temporal phases. In the acute phases (for about three days), T1 and T2 times are relatively long. In the subacute phase (approximately three days to two weeks), the T1 time shortens, producing a strong signal on T1-weighted scans. This phenomenon is thought to be due to oxidative denaturation of hemoglobin, resulting in the formation of methemoglobin, a strongly paramagnetic substance that shortens the T1 relaxation time.[10,11] After about two weeks, as methemoglobin is resorbed, the T1 time lengthens. When blood collections are in the isodense phase in CT, MR imaging can be very helpful in establishing the diagnosis (Figure 2).

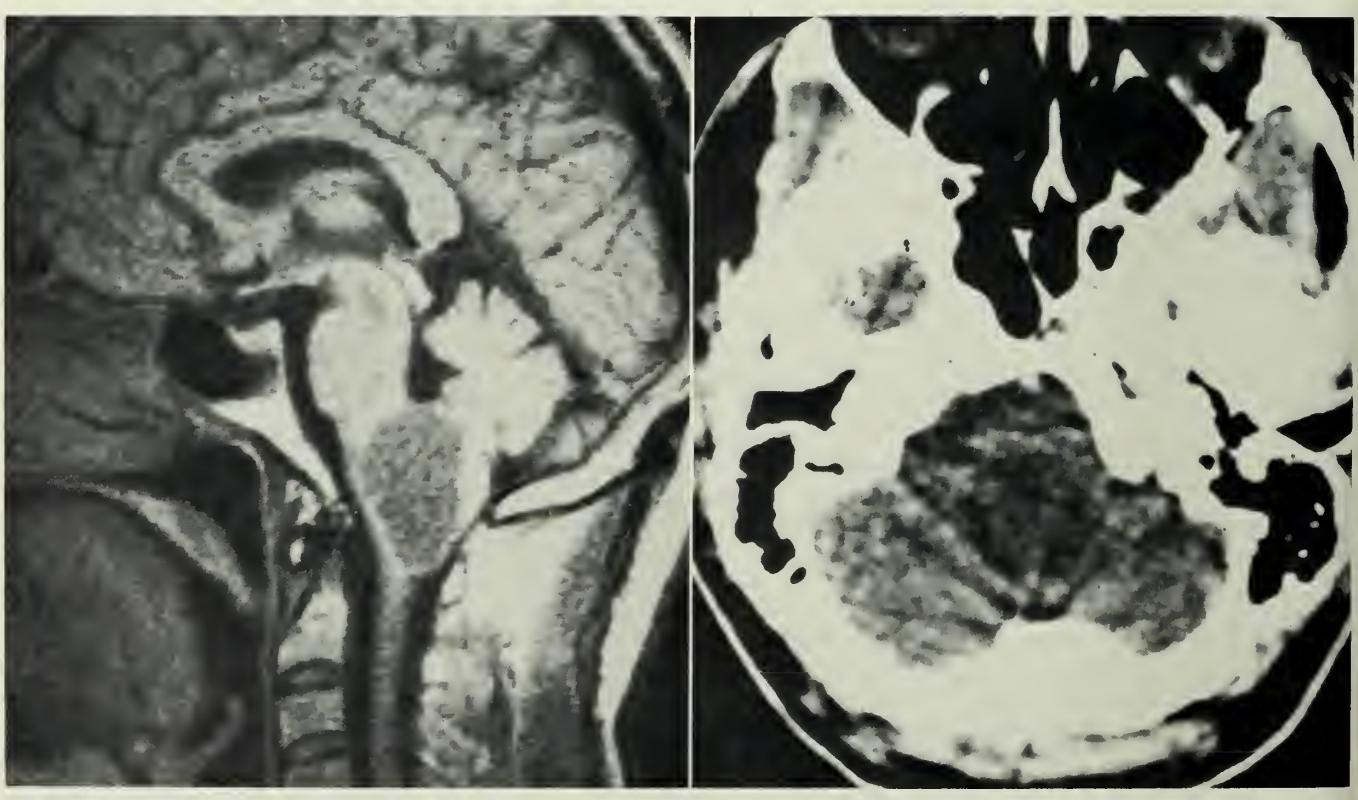

Figure 1.—Left, spin echo techniques (echo time, 30 ms); repetition time, 600 ms. Sagittal view through the midline of the brain showing extension of a cystic astrocytoma involving the medulla and upper cervical cord. **Right,** A computed tomographic scan through the posterior fossa of the same patient shows a hypodense area blurred by streak artifact as a result of the thickness of the skull in this region.

Vascular Disease

In both subacute and acute phases, infarcted brain tissue is characterized by increased T1 and T2 times. The infarcted area has sharp margins and yields an intense signal in T2-weighted images and a weak signal in T1-weighted images.[12] After a few days, a hemorrhagic infarct yields an intense signal in T1-weighted scans because of the presence of blood. In the chronic phase, infarcts have two distinct appearances: either a central area of low signal intensity with a peripheral zone of higher intensity, or as an area of cerebrospinal fluid (CSF) intensity without a peripheral zone of higher intensity.[12]

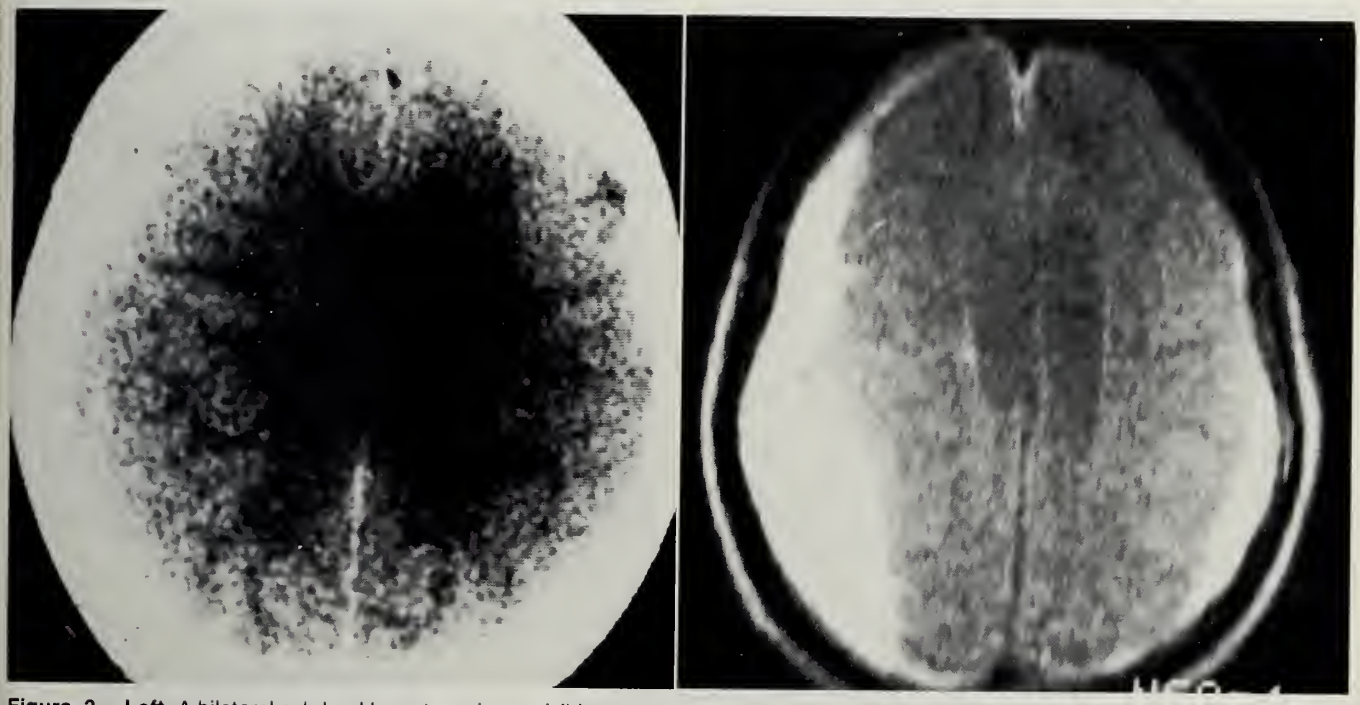

Figure 2.—Left, A bilateral subdural hematoma is not visible on a computed tomographic scan as its density is similar to that of brain tissue. **Right,** The bilateral hematoma is depicted better on magnetic resonance imaging with a long spin-echo sequence.

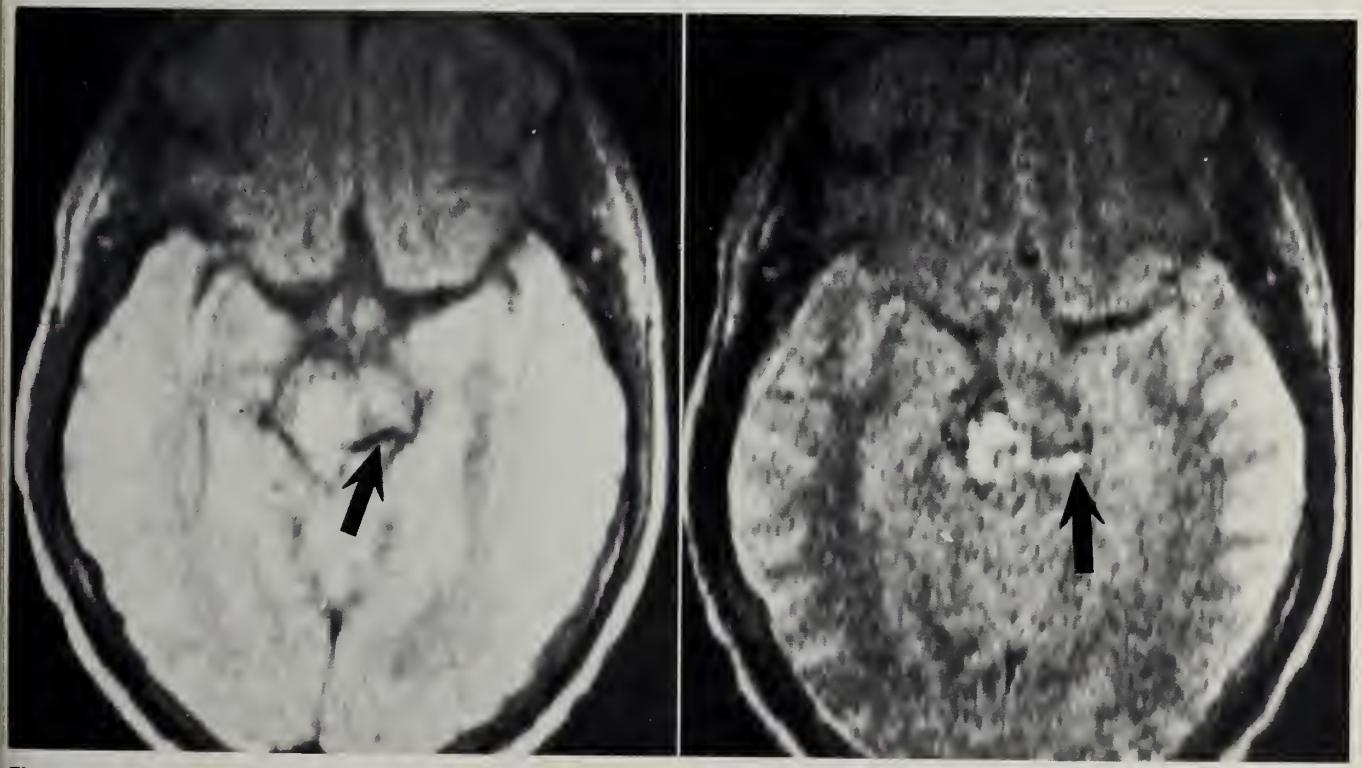

Figure 3.—Even-echo rephasing phenomenon on magnetic resonance imaging. A hemorrhagic arteriovenous malformation involving the right cerebral peduncle is shown by a multiecho sequence. The draining vein is dark on the first echo **(left arrow)** and bright on the second echo **(right arrow)**.

An arteriovenous malformation has slow venous flow; hence, a multiecho sequence displaying increased signal intensity during each even echo is often taken as diagnostic for an arteriovenous malformation.[13,14] Waluch and Bradley have termed this phenomenon "even-echo rephasing in slow laminar flow" (Figure 3).[15] Three factors contribute to this phenomenon: the slow laminar flow in a vessel, the gradient present in the magnetic field and the spin-echo technique used. Following the 90° pulse, the signal produced after the first 180° pulse (odd echo) is weak because the spins have not completely rephased. The signal produced after the second 180° pulse (even echo) is stronger because the spins have completely rephased. Hemorrhagic arteriovenous malformations display a high signal intensity in a T1-weighted scan after a few days.

Sellar and Parasellar Regions

In the sellar and parasellar regions, one principal advantage of MR imaging is its lack of bone artifacts. Mark and colleagues[16] have reported that the pituitary yields a moderate signal, similar to that from the pons. A low signal from the pituitary may reflect partial volume averaging with vascular channels lateral to the gland. The high signal intensity near the posterior and inferior regions of the gland is contributed by fatty marrow in the posterior clinoid processes. A small fat pad is also present in the posteroinferior aspect of the sella.[16] The lamina dura defining the pituitary inferiorly yields no MR imaging signal and appears dark when the sphenoid sinus is incompletely pneumatized. With thinner slices and better spatial resolution, MR imaging should become the first investigative procedure when a pituitary tumor is suspected. Involvement of the optic tract and the optic chiasm and the suprasellar extent of the tumor can be appreciated on sagittal T1 images. Chromophobe and prolactin adenomas have long T1 and T2 relaxation times and therefore appear dark on T1-weighted images and bright on T2-weighted images. Craniopharyngioma is better evaluated by CT because calcifications, which are important for the diagnosis, do not return an MR imaging signal.

Craniocervical Junction

Magnetic resonance imaging depicts the craniocervical junction with considerable definition. Sagittal views provide direct visualization of the brain stem, cerebellar tonsils and upper cervical spine, with a resolution significantly superior to that of reformatted sagittal CT views. Abnormal conditions visible on MR images include basilar invagination due to conditions such as rheumatoid arthritis and Paget's disease, tumors such as clival meningiomas and brain-stem gliomas, basilar tip aneurysms, arachnoid cysts, Arnold-Chiari malformations and syringomyelia.

Spine

Magnetic resonance imaging is rapidly becoming the preferred method for examining the spinal canal and cord. A short spin-echo technique yields sharp contrast between the spinal cord and the subarachnoid space; cortical bone and CSF are not separable, however. Vertebral bodies yield a strong signal because of the presence of marrow, with its short T1 time. A long spin-echo technique emphasizes T2 and increases the signal from the normal nucleus pulposus and CSF. With a long echo time (120 ms) and a long repetition time (2,000 ms), one can obtain images with contrast comparable with that of a myelogram.[17]

Extradural lesions. Disk degeneration is usually identified in an earlier stage by MR imaging than by CT[17]; small and lateral herniations, however, are sometimes diagnosed better with CT.[17] T2-weighted images separate the normal nucleus pulposus from the annulus and degenerated disk and permit identification of medial disk herniation and canal stenosis (Figure 4).[17]

In the vertebral disk in the young, MR imaging can differentiate between nucleus pulposus and annulus because they have a different water content. This difference decreases with age, leading to a diminution in the signal difference between the two structures.

MR imaging is as accurate as CT and myelography in the depiction of canal stenosis and shows the caudal and cranial extent of the stenosis in the case of complete block.[17]

Neoplasms involving the vertebral bodies yield a reduced signal in T1-weighted images and an increased signal in T2-weighted images.[17] These properties permit a clinician to differentiate between degenerative changes and metastases in some cases. Because of blood flow, hemangiomas usually remain dark in both T1- and T2-weighted sequences. If the flow rate is slow enough, however, hemangiomas can yield high signal intensity in T1-weighted images.

In irradiated vertebrae, fatty degeneration yields an increased signal in T1-weighted images (Figure 5).

Magnetic resonance imaging is an excellent modality for evaluating fractures that may encroach on the subarachnoid

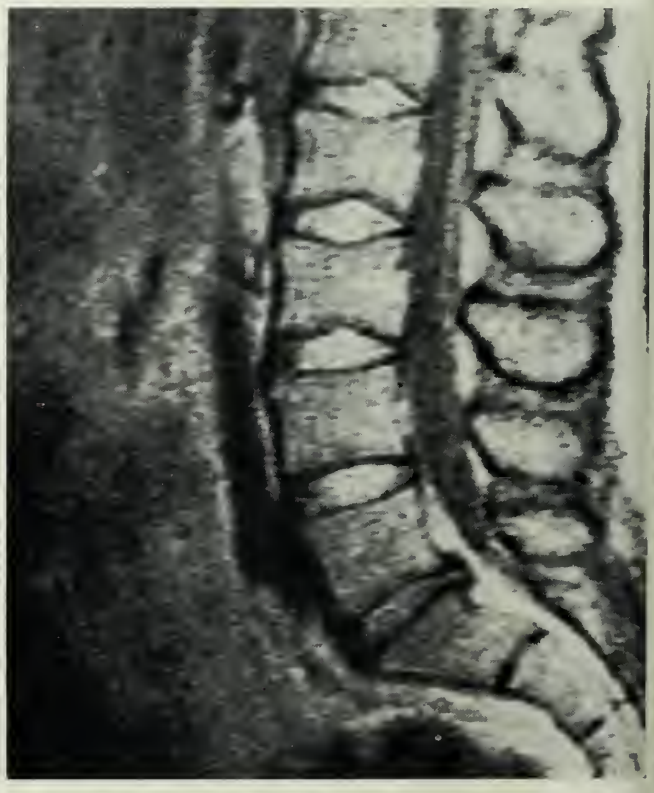

Figure 4.—Multiecho sequence (echo time, 30 and 60 ms; pulse repetition time, 1,500 ms). A central bulging disk at L5-S1 is pushing on the predural sac fat.

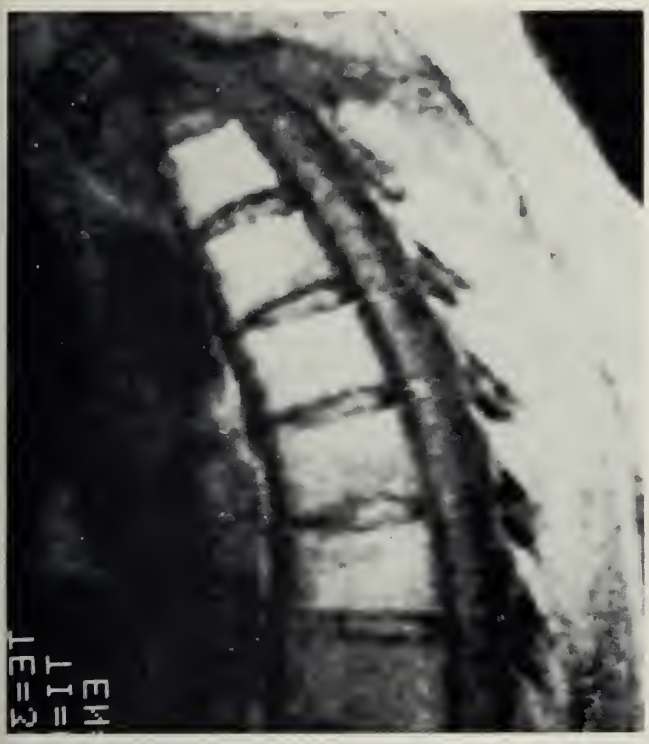

Figure 5.—Fatty degeneration after radiation therapy. A spin-echo sequence using an echo time of 30 ms and a pulse repetition time of 500 ms yields increased signal from several vertebral bodies with fatty replacement of the normal bone marrow after radiation therapy.

space and cord. Although bone fragments do not return a signal, acute secondary hemorrhage within the spinal canal and neural foramina follows the pattern of extravascular blood elsewhere and can be evaluated.

For a display of infection, MR imaging is more sensitive than plain films or CT and as sensitive as and more specific than radionuclide studies.[17] Diskitis is characterized by increased T1 and T2 times and involves the disk and the endplates. Degenerative changes have a short T2.[17]

For evaluation of subluxation, sagittal views can be taken in extension and flexion. This relatively dynamic study shows the relationship between the cord and bony structures and is particularly useful for diagnosing C-1 and C-2 subluxation, rheumatoid arthritis, basilar invagination and postoperative bony fusions.

Intradural lesions. Lipomeningoceles are displayed well with MR imaging because lipomas yield a very strong signal in T1-weighted images. This condition is often associated with a tethered cord, which is also easily depicted.[18] Meningiomas have a long T1 and a variable T2; compression of the cord by these tumors is shown well with MR imaging. Lymphomas have long T1 and T2 times. Because of this, the margins of the cord often are not well delineated on T1-weighted images. Metastases have long T1 and long T2 times, with the exception of melanoma metastases. These may yield a high signal intensity on T1-weighted images because they are hemorrhagic or contain melanin (which is paramagnetic), or both. Many primary tumors have long T1 and T2 relax-

Figure 6.—Cord tumor. **Left,** A T1-weighted image (echo time [TE], 30 ms; repetition time [TR], 500 ms) using a spine surface coil. The cord is enlarged. **Right,** In a T2-weighted scan (TE, 75 ms; TR, 1,500 ms), the cord has an abnormally intense signal because of the prolonged T2 of the tumor.

ation times, yielding a high signal intensity on T2-weighted scans. Often the tumor enlarges the cord, a finding best depicted on T1-weighted scans (Figure 6).

Magnetic resonance imaging is an accurate and sensitive method for detecting cystic cavities such as those of syringomyelia, hydromyelia and progressive posttraumatic cystic myelopathy. On T1-weighted scans the cavity appears as a region of decreased signal, identical to that of the CSF. On T2-weighted images the adjacent cord might have an increased signal intensity as a result of myelomalacia.

Demyelinating diseases such as multiple sclerosis yield an increased signal intensity when a long spin-echo technique is used; the increase is caused by the prolonged T2 of the abnormal areas. MR imaging is a very sensitive technique for depicting these conditions.

With MR imaging, a divided spinal cord (diastematomyelia) is well imaged over its entire craniocaudal extent. When the bony septum contains marrow, it also is visible.[19]

Pediatric Applications

Magnetic resonance imaging is a sensitive technique for detecting deficient or delayed myelination of the brain in children. Inversion recovery seems to be the most sensitive technique because it optimizes the contrast between grey and white matter.[20]

Parenchymal and subependymal hemorrhages are easy to recognize 48 hours after they occur because they yield an intense signal on a T1-weighted scan. Before 48 hours they have long T1 and T2 times.[20] Porencephalic cysts, a late finding following hemorrhage, have T1 and T2 relaxation times as long as those of ventricular CSF if the cyst communicates with the arachnoid space, thereby permitting differentiation of this condition from acute hemorrhage.

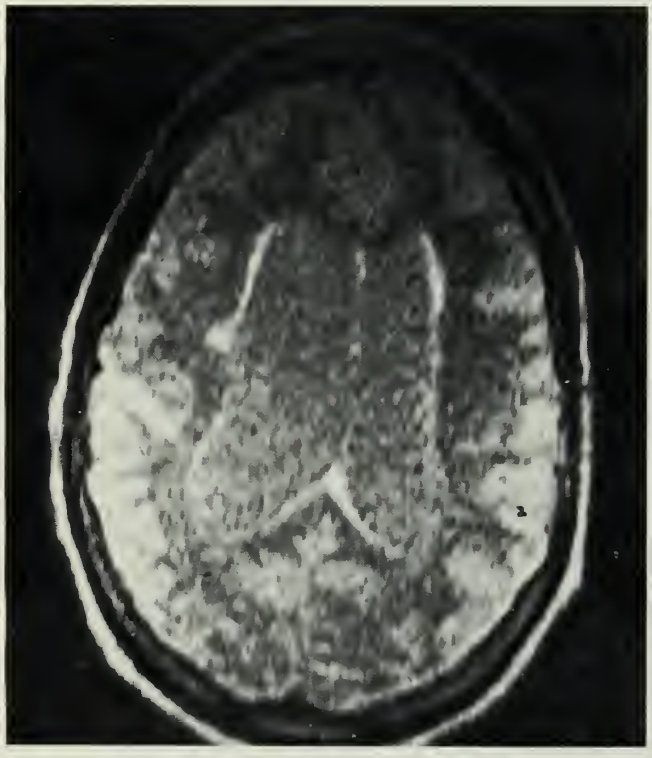

Figure 7.—Obstructive hydrocephalus due to a colloid cyst of the third ventricle. A T2-weighted scan shows abnormal signals surrounding the ventricles as a result of transependymal flow of cerebrospinal fluid.

Hydrocephalus is easy to detect on a T1-weighted scan. If it is obstructive, it is accompanied by transependymal flow at the margin of the ventricular system, which is visualized as a region of prolonged T2 surrounding the enlarged ventricles (Figure 7). After shunt placement, MR imaging often shows a reduction in the ventricular size and in the surrounding edema.[20]

Congenital abnormalities such as semilobar holoprosencephaly, septo-optic dysplasia, absence of the septum pellucidum, corpus callosum aplasia and dysplasia and aqueductal stenosis are detectable with MR imaging after the fontanelles have closed and ultrasonography is no longer useful.[20]

Ischemic anoxic encephalopathy with extensive areas of damage in the white matter is depicted by MR imaging. In neonatal hypoxia, phosphorus spectroscopy can show cerebral ischemia before this condition is detectable with ultrasound or CT studies.[21]

Cerebral palsy yields an increased signal in the anterior periventricular regions.[20]

Head

Temporomandibular Joint

The main advantage of MR imaging of the temporomandibular joint is its provision of sagittal and coronal views and its superb soft tissue contrast. Its ability to image the disk and surrounding tissues is particularly useful.[22] The use of surface coils and thin slices may facilitate replacement of CT and arthrography by MR imaging.[22]

Orbit

The orbit is well suited to examination by MR imaging because of the presence of retrobulbar fat. Because the MR imaging signal depends on the water and protein content of a structure, the lens is well differentiated from vitreous fluid. On the other hand, the sclera and cornea are difficult to identify, partly because of the motion of the globe.[23] The use of surface coils greatly improves the signal-to-noise ratio, and thinner slices provide better spatial resolution.[24]

Choroidal melanoma yields a strong signal and is recognizable with little difficulty by MR imaging. The high signal intensity is explained by a short T1 relaxation time that is related to the paramagnetic properties of melanin.[23] Retinoblastoma is well shown by spin-echo sequences with both short and long repetition times.[24]

Manifestations of orbital pseudotumor vary from vasculitis to fibrotic sclerosis to generalized lymphocytic infiltration.[23] The increased water content lengthens the T1 time so that the lesion appears dark on T1-weighted scans.

Thyroid ophthalmopathy is caused by deposition of mucopolysaccharides, infiltration of plasma cells and lymphocytes and an increase in the orbital connective tissue.[23] In this condition the T1 and T2 values are prolonged in contrast to the short T1 of fat.

Most tumors involving the lacrimal fossa, such as adenoid cystic carcinoma, metastatic adenocarcinoma and lymphoma, have prolonged relaxation values, making them indistinguishable from each other by MR imaging.[24] A dermoid tumor from a patient in the series reported by Sobel and associates[24] had a short T1 because of the presence of fat, and a more

specific diagnosis could be made. With thinner slices and surface coils for the orbit, MR imaging should become very useful in distinguishing optic nerve gliomas and neuritis. The ability of MR imaging to differentiate normal and pathologic orbital tissue is equal to that of CT.[23] However, MR imaging is more sensitive than CT in depicting intraorbital hemorrhage and ischemia of the globe.[25]

Nasopharynx

Tumors producing mass effects are well delineated by MR imaging because of the displacement of fat in the nasopharynx. A long repetition time (T2-weighted scan) is usually used to differentiate muscle from tumor and to enhance visualization of the tumor. Detection of adenopathy is important for defining nasopharyngeal carcinoma; MR imaging can clearly differentiate adenopathy from muscle because involved lymph nodes produce a stronger signal. The retropharyngeal space lies between the pharyngobasilar and prevertebral fasciae; in normal conditions it is not visible either by MR imaging or CT. In pathologic conditions such as nasopharyngeal carcinoma, adenopathy can be detected in this region.[26]

The base of the skull requires careful analysis because tumor usually grows upward along fascial planes in the nasopharynx to this region. Sagittal MR imaging views show tumor extension through the clivus and depict involvement of the sphenoid sinus (Figure 8). The clivus produces a strong signal on all pulse sequences because of its marrow content. The sphenoid sinus has no signal because of its aeration; therefore, inflammation and tumor extension are well depicted by MR imaging. Dysfunction of the eustachian tube, otitis media or mastoiditis on the ipsilateral side is often associated with neoplastic processes of the nasopharynx. These lesions produce an intense signal that is easy to recognize in transverse views.

Salivary Glands

Parotid tumors (adenocystic carcinoma and sarcoma) and submandibular gland carcinomas have prolonged T1 and T2 values that are different from normal glandular tissue and adjacent muscles and fat.

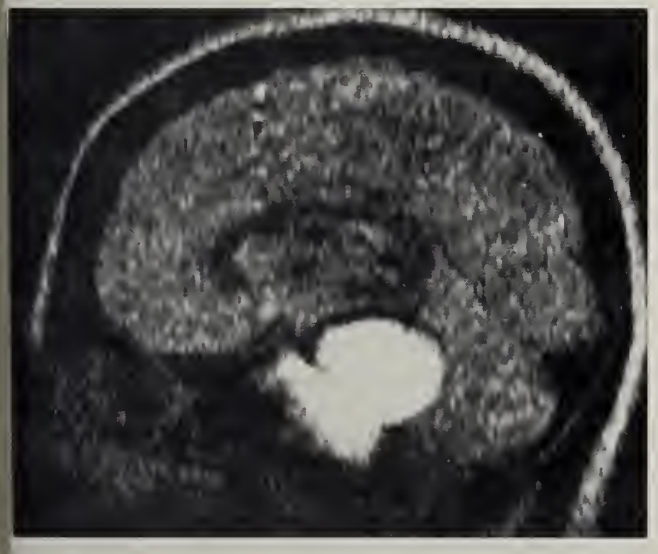

Figure 8.—A T2-weighted scan shows a chordoma involving the clivus and extending to the posterior fossa.

Neck

Although the spatial resolution of MR imaging is slightly inferior to that of high-resolution CT,[27] the greater contrast resolution of MR imaging and its flexibility with regard to transaxial, coronal and sagittal imaging permit excellent differentiation of normal tissues, tumors, lymph nodes, muscles and blood vessels.[27] Elliptical radio-frequency coils can be used to increase the signal-to-noise ratio when this anatomic region is imaged with magnetic resonance.

Thyroid nodules, cysts and normal tissue usually can be differentiated in MR images.[28] Thyroid cysts have the greatest water content and the longest T1 and T2 relaxation times.[28] Parathyroid adenomas may have slightly longer relaxation times than those of a hyperplastic parathyroid gland; this finding has not been confirmed in duplicated studies, however.[28]

Generally, abnormal lymph nodes have increased T1 and T2 times. MR imaging has advantages over CT in differentiating enlarged lymph nodes from muscles and from tortuous vessels in the neck.[28] The signal intensity of scar tissue does not increase significantly when the repetition time is increased; consequently the T2 time of scar tissue appears to be short relative to other tissues and to recurrent tumor.[28] Tumors involving the laryngeal tract and their extension into the parapharyngeal space are well depicted by MR imaging.

Mediastinum and Chest

It is relatively easy with MR imaging to differentiate masses (either adenopathy or extension of bronchogenic carcinoma) from vascular structures in the chest because flowing blood provides high intrinsic contrast. To differentiate mediastinal fat from tumor, T1-weighted images are used. In these images, the tumor mass will be dark (a long T1 time) and the fat will be bright (a short T1 time). Because of overlapping relaxation times, T1 and T2 computations do not permit differentiation of sarcoidosis from lymphoma.[29] MR imaging depicts enlarged tortuous vessels without difficulty.

Compared with CT, MR imaging has inferior spatial resolution because it uses thicker slices and is more vulnerable to cardiac and respiratory motion. Cardiac gating improves resolution but increases scan duration. Nevertheless, in many cases MR imaging shows differences between small vessels and abnormal nodules better than does CT. In the future, MR imaging may permit quantification of lung fluid, making it useful in the management of pulmonary edema and hemorrhage.[30] Early experimental work suggests that MR imaging may be useful in showing distal pulmonary emboli (high signal intensity on T1-weighted images). Proximal pulmonary emboli sometimes are misinterpreted as mediastinal fat.[31]

Magnetic resonance imaging has considerable potential for detecting pulmonary diseases in children. On chest roentgenograms it can be difficult to differentiate normal pulmonary vessels from adjacent linear atelectasis, bronchi with mucoid impaction and peribronchial inflammatory changes. This problem led Gooding and associates to compare MR imaging with CT and chest roentgenography in six children with cystic fibrosis.[32] More mucoid plugs were evident with MR imaging than with chest roentgenography, and more mediastinal nodes were apparent with MR imaging than with CT. In children with cystic fibrosis, MR imaging showed a

shrunken pancreas that yields a strong signal as a result of fatty replacement.[32] Gooding and co-workers suggest that MR imaging may become the principal imaging modality in patients suspected to have cystic fibrosis.[32]

Cardiovascular Systems

Ungated cardiac images are subject to considerable resolution loss due to motion; the images are improved significantly by gating. Cardiac images with excellent spatial resolution can be obtained by gating at various times within the cardiac cycle, at the expense of a slight increase in imaging time. In the case of septal defects, atrioventricular canal defects are shown well by MR imaging, as are ventricular septal defects. MR imaging permits assessment of atrioventricular valve morphology, chamber sizes and ventricular wall thickness.[33] Ventricular hypoplasia is well depicted, and signal analysis of the myocardium can be helpful in showing fatty replacement. T1-weighted scans are the most widely used gated cardiac images.[33]

Various valvular diseases are successfully shown by MR imaging. In aortic stenosis, for instance, valves appear thicker and have decreased mobility; they sometimes are visible in systole, whereas normal valves are not visible in this phase. Great vessel abnormalities are often recognizable (Figure 9), although identification of specific structures is sometimes difficult.[33] Palliative systemic pulmonary artery shunt normally is free of signal, indicating flowing blood. A clot in the shunt appears bright, as does turbulent and slowly flowing blood.

MR imaging may show the presence of myocardial infarction because the signal intensity of the infarcted region is higher (prolonged T2 time) than that of the surrounding normal myocardium.[34] Magnetic resonance spectroscopy of endogenous phosphates in the myocardium may eventually permit assessment of the functional integrity of myocardium.[35] Paramagnetic intravenously administered contrast agents that shorten T1 and T2 relaxation times could be useful for early detection of myocardial ischemia in the future. Manganese ions (^{52}Mn and ^{54}Mn) are distributed in the myocardium in proportion to blood flow. Consequently, ischemic myocardial regions show a deficiency in Mn^{++} distribution.[35] In patients with cardiac failure, slowly flowing blood in the ventricle produces a high signal intensity. Ventricular aneurysms are also shown by slow and turbulent blood flow and by thinning and bulging of affected cardiac wall.

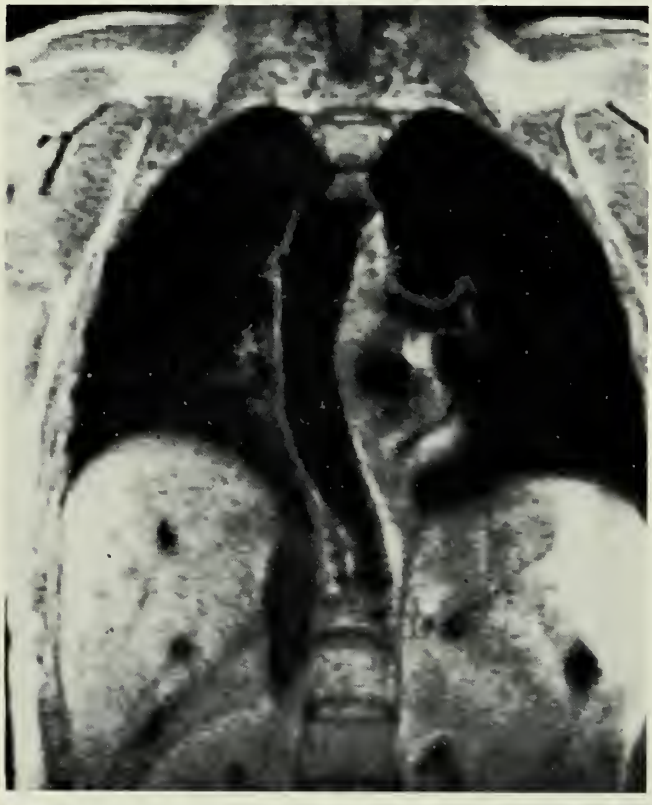

Figure 9.—A gated cardiac scan, coronal view, depicting a right descending aorta.

Magnetic resonance imaging promises to become an important modality for evaluating pericardial disease. It can differentiate simple pericardial cysts from pericardial masses, fat and diaphragmatic eventration.[36] MR imaging shows normal pericardium as a 1- to 2-mm thick curvilinear structure of low signal intensity.[36] Changes in this configuration occur in constrictive pericarditis, inflammations and effusions.

Cardiac tumors are identifiable as thickening of the chamber wall, with decreased systolic ejection volume and abnormal signal intensity from the tumor.

The contrast between flowing blood and vessel wall permits evaluation of several vascular diseases. The signal from flowing blood is highly dependent on the pulse sequence and pulsing times chosen for the study. Atherosclerotic plaques are dark when they contain connective tissue, and they are surrounded by high signal intensity caused by lipid accumulation. Calcifications are frequently not detected as they produce no signal.[37]

Magnetic resonance imaging can show aneurysms and aortic dissections without a contrast agent. Coronal and sagittal views show the extent of these conditions and whether they involve the renal arteries. True and false channels are recognizable. Thrombus, slow laminar flow and turbulent flow can all produce increased signal and may be difficult to differentiate from each other. Because the MR imaging signal depends on flow velocity, there is considerable interest in calculating flow velocities from MR measurements.

Breast

The breast is a heterogeneous organ composed of fat, epithelial tissue and fibrous stroma in different proportions. Fat is readily differentiated from other tissues by MR imaging and produces a strong signal because of its short T1 time. The T1 time of ducts and fibrous stroma varies with the menstrual cycle and with the use of exogenous hormones. Age and pregnancy also affect the T1 value. In a study by McSweeney and associates, discrimination based on T2 values could differentiate benign lesions from carcinoma in specimens that contained tumor and fat or tumor and a mixture of fat and fibrous tissue.[38] There was overlap of T2 values in specimens containing tumor and predominantly fibrous tissue. Cysts are well visualized, but calcifications are not seen. Paramagnetic contrast agents conjugated with specific monoclonal antibodies are being investigated in an effort to increase the sensitivity and specificity of MR imaging for breast cancer detection. MR imaging may be useful in staging breast tumors

because of its ability to detect axillary and supraclavicular adenopathy and chest wall involvement by tumor.

Abdomen

Respiratory gating of abdominal MR imaging scans has improved spatial resolution in some cases. In this process, information is acquired only between the end of expiration and the beginning of inspiration, so that motion artifacts are reduced. Scan time is significantly increased, however.

Magnetic resonance imaging is very sensitive to liver disease. However, the signal intensity of tumors varies strongly with the pulse sequence used.[39] The T1 and T2 values of different liver tumors extend over a rather narrow range, and MR imaging has difficulty differentiating between benign and malignant processes. Paramagnetic agents could help increase MR imaging sensitivity dramatically for liver disease. MR imaging appears to be more definitive than CT in showing the internal architecture of a liver mass, its extent and its relationship with vascular structures.[39] Some authors have reported that T2 is longer for neoplastic processes than for normal liver and that pulse sequences which emphasize differences in T2 values might show liver lesions earlier.[40] With the development of spectroscopy, magnetic resonance could gain greater specificity by identifying metabolic changes in affected tissues.

In diffuse liver disease MR imaging has an important role. It detects hepatitis and cirrhosis because the T1 value of affected tissues is longer than that of normal liver. In hemosiderosis and hemochromatosis, the T1 value is decreased due to the presence of paramagnetic iron deposits.[41,42]

The pancreas is difficult to image with any imaging modality, including magnetic resonance. One advantage of MR imaging is the lack of bone- or gas-induced artifact. Smith has reported that differences in the T1 of normal and cancerous pancreas may give MR imaging an advantage over ultrasound, CT and nuclear medicine.[43] Margins of pancreatic pseudocysts are often shown better by CT than by MR imaging.[44]

Transverse and coronal views nicely show both kidneys. T1-weighted inversion recovery images yield excellent corticomedullary differentiation.[45] Cortex and columns of Bertin are light-grey because of their relatively short T1 value, whereas the medulla is dark because of its longer T1 time. Perirenal fat provides a strong signal that delineates both kidneys and permits evaluation of the extracapsular extension of a renal tumor. MR imaging is able to differentiate cystic from solid masses and to depict fatty components within the lesion. Tumor extension into or around renal veins and arteries, inferior vena cava and aorta is best evaluated using transverse and sagittal views.

Renal failure is accompanied by a loss of corticomedullary differentiation. This observation is helpful in evaluating renal function. The loss of corticomedullary differentiation is also seen in acute and chronic rejection. However, acute rejection is accompanied by a low signal intensity from the transplanted kidney.[46] In acute tubular necrosis the corticomedullary differentiation is variable.[46]

Magnetic resonance imaging is sometimes helpful in detecting abnormal adrenals; in general, however, there appears to be no significant improvement over CT.[47] Although small calcifications are not detected, MR imaging is useful for visualization of adjacent major vascular structures.[47] In some cases, adrenal hyperplasia is shown as an inner region of low intensity surrounded by an outer region of higher intensity.[47]

In children, abdominal masses present a diagnostic challenge. MR imaging shows tumor spread to bone marrow, liver and abdominal lymph nodes and demonstrates vessel encasement, the major factor limiting surgical resection.[48] In children with neuroblastoma, Cohen and colleagues found MR imaging to be very helpful in showing metastatic disease and in aiding the prediction of tumor resectability.[48] Neuroblastoma shows prolonged T1 and T2 times. On a T1-weighted scan, therefore, neuroblastoma appears darker than adjacent liver and muscle, whereas on a T2-weighted scan the tumor signal is increased. MR imaging can be used to monitor the response of neuroblastoma to chemotherapy and radiation therapy.[48] A major disadvantage of MR imaging is that calcifications are not seen. This limitation makes it difficult to differentiate neuroblastoma from Wilms' tumor.

Pelvis

The pelvis is depicted well by MR imaging because of the high level of contrast provided by pelvic fat, urine in the bladder and gas in the bowel. There is little blurring caused by motion, and the large amount of bone in this region does not interfere with MR imaging.[49,50] Images are acquired in transverse, coronal and sagittal planes. In a spin-echo sequence, the uterus, prostate and seminal vesicles have a slightly higher signal intensity than do the skeletal muscles.[50]

For a clear distinction of ovary from surrounding adipose tissue, a short spin-echo technique is preferred.[51] Ovarian cysts yield variable signal intensities that depend on their protein and cholesterol content.[50] Unfortunately, some large serous cystadenomas have the same signal intensity as urine. In papillary cystadenofibroma, the cystic portion yields an intense spin-echo signal, indicating a long T1 time, whereas the solid portion has the appearance of muscle (dark).[52] Dermoid tumors contain considerable fat and yield a high signal intensity in all sequences because of a short T1 and moderate T2 value. Some areas may remain dark because of the presence of calcific material.

Sagittal as well as transverse images are used to show the uterus.[50] The endometrium yields a stronger MR imaging signal than does the myometrium, which in turn is slightly stronger than the striated muscle of the pelvic wall. The myometrium and endometrium are separated by a low signal line, probably the stratum basale.[51] The endocervix may have a high signal intensity because of the presence of mucus.[51] Leiomyomas are differentiated from normal uterus by increases in both T1 and T2 times and by their presentation as homogeneous masses. With a short spin-echo technique, endometriosis may provide an increased signal intensity due to the presence of hemorrhage.[52] Endometrial carcinoma has prolonged T1 and T2 relaxation times and appears as an inhomogeneous mass because of necrotic areas.[50]

The vagina usually provides a weaker signal than does the uterus.[51] MR imaging provides important information regarding the anatomic relationship of the vagina, bladder and rectum.

The normal prostate gland is homogeneous and has a medium signal intensity, which increases slowly as the repetition time increases.[53] Calcifications yield no signal. Benign hy-

pertrophy of the gland has a tendency to elevate the floor of the bladder; this is best shown on coronal or sagittal images.[50] Prostatic carcinoma is presented as an inhomogeneous mass.[54,55] When a short spin-echo sequence is used, malignant nodules yield a weaker signal than does the normal gland. A strong signal is sometimes present as a result of intratumoral hemorrhage.[53] Tumor extension is apparent because the normal gland is surrounded by a pencil-thin rim of lower intensity and by pelvic fat in the space of Retzius. This fat can be distinguished easily from the pelvic prostatic ligament.[53] The prostate, rectum and levator ani muscles are all easily distinguished. Because the seminal vesicles are bright in a long spin-echo sequence, their gross involvement in prostatic cancer is easy to detect.[53] Prostatitis and carcinoma have overlapping relaxation times.[54]

Magnetic resonance imaging is an excellent method for investigating bladder disease. The urine in and the fat surrounding the bladder permit clear delineation of this structure. Normal bladder wall is thin and identifiable as a discrete structure.[50] Wall thickening by chronic obstruction is readily detected, as is carcinoma, which produces a bright signal when a long pulse sequence is used. Extravesical extension into the perivesical fat is generally more obvious with MR imaging than with CT.[56] MR imaging has already assumed a prominent role in the clinical evaluation of carcinoma of the bladder and prostate.[53]

Musculoskeletal System

Magnetic resonance imaging is the method of choice in the diagnosis of avascular necrosis of the femoral head. In their comparative study of 38 healthy subjects and 20 patients with abnormalities, Totty and associates showed that MR imaging was superior to both roentgenography and scintigraphy in depicting this condition.[57] The normal femoral head is surrounded by a thin low-intensity cortex. With all pulse sequences, the medullary cavity has a strong signal intensity emanating from the large deposits of fat and from hematopoietic cells. Regions of reduced intensity crossing the high-intensity cavity are due to the physis (transversally oriented) and the weight-bearing trabeculae (vertically oriented). Between 12 and 48 hours after an ischemic insult, the signal becomes very low because of the death of osteocytes, hematopoietic cells and, eventually, fat cells in the infarcted region.[57]

Magnetic resonance imaging can be used to evaluate ligamentous tears after acute knee injury. Sagittal and parasagittal views show the cruciate ligaments, and coronal views show the tibial and fibular collateral ligaments. On T2-weighted images, high signal intensity between the medial collateral ligament and the medial meniscus is considered diagnostic of a torn medial collateral ligament.[58]

Because of its exquisite soft tissue differentiation, MR imaging can be used to detect bone tumors and to evaluate the extension of the tumor into adjacent soft tissue and bone marrow. MR imaging provides high-resolution images of extremities and shows tumor by changes in both anatomic structure and relaxation time.[59]

Conclusion

Magnetic resonance imaging is already an important and useful clinical tool because it uses no ionizing radiation. Its safety and sensitivity suggest that it may replace many invasive and risky techniques such as myelography. This new imaging modality has become competitive with computed tomography. The use of paramagnetic contrast agents, thinner slices and surface coils will add more specificity and will provide better spatial resolution. Spectroscopy promises detection of early pathologic changes in metabolism.

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Strategies for Treating Autoimmune Disease With Monoclonal Antibodies

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There is no safe and reliable therapy for most serious autoimmune diseases, such as systemic lupus erythematosus. Severe cases usually require treatment with corticosteroids or cytotoxic drugs or both, which frequently provide inadequate disease control and can cause serious complications. These therapies are not restricted in their effects to cells of the immune system, but rather have a broad range of toxic effects on cells throughout the body. The development of monoclonal antibodies has led to new therapeutic strategies through which treatment can be focused more directly on specific cells (and functions) of the immune system. These strategies have already produced promising results in animal models for several important human autoimmune diseases. We will know soon whether treatment with monoclonal antibodies will be effective in persons with autoimmune disease.

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It has long been recognized that certain antibodies can be used as immunosuppressive agents. For example, antilymphocyte serum and antithymocyte serum have been used for many years to deplete immunocompetent cells and thereby facilitate organ transplantation. Although useful, these antiserums are far from ideal. They are not restricted in their reactivity to distinct lymphocyte subsets, but rather react with a broad range of antigens on several different cell types, including some nonlymphoid cells. Moreover, these antiserums generally elicit a host immune response that may limit their efficacy and lead to adverse reactions such as serum sickness.

Recent advances in biotechnology have improved significantly on the conventional antiserums of the past. It is now possible to produce virtually unlimited quantities of specific homogeneous antibodies, called "monoclonal antibodies." These antibodies have added immeasurably to our ability to identify and selectively bind distinct cells of the immune system. As a result, monoclonal antibodies can be used to manipulate the immune system in ways that were not previously possible. This achievement has led to the development of several new strategies for the treatment of autoimmune disease, which have already been effective in experimental animals with autoimmune disease, and they will soon be tested in people.

Production of Monoclonal Antibodies

The idea of using antibodies to focus therapy on cells with specific surface antigens is not new. Paul Ehrlich first conceived of the idea almost a century ago when he considered using antibodies as "magic bullets" that might be effective not only against bacterial cells but also against cancer cells.[1] Until recently, it was impossible to achieve this goal because normal B lymphocytes, with the capacity to produce specific antibodies, would not survive long term in culture. Only malignant cells, such as multiple myeloma cells, could be maintained perpetually in vitro as cultured cells. In 1975, however, George Kohler and Cesar Milstein developed techniques through which they could generate cells that possessed the specific antibody-producing characteristics of a normal lymphocyte and the "immortal" characteristics of a myeloma cell.[2] Individual clones derived from these unique cells could survive in culture and produce large quantities of identical (monoclonal) antibodies. For this contribution, Kohler and Milstein were awarded the 1984 Nobel prize for medicine.

The principles involved in producing monoclonal antibodies are illustrated in Figure 1. First, an animal (usually a rodent) is immunized with the antigen(s) against which one would like to have a monoclonal antibody. As a consequence, lymphocytes capable of producing antibodies to the anti-

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ABBREVIATIONS USED IN TEXT

B/W mice = hybridized New Zealand black and New Zealand white mice
HLA = human leukocyte antigen
Ia = immune-associated [antigen]
Ig = immunoglobulin
MHA I or II = major histocompatibility antigens, class I or II

gen(s) proliferate in the spleen of the animal. The spleen cells are then removed and incubated with myeloma cells in the presence of an agent that facilitates fusion of cell membranes. Under these conditions, some spleen cells fuse with myeloma cells, producing hybrid cells that may retain the antibody-producing capacity of the spleen cell and the immortal quality of the myeloma cell. Clones derived from such hybrid cells are referred to as "hybridomas." To simplify recognition of these hybridomas, mutant myeloma cells are used that do not secrete their own immunoglobulin and that lack an enzyme (hypoxanthine phosphoribosyl transferase) that is required for their growth in certain media. The fusion can therefore be conducted in media that will support the growth of hybridoma cells only. These cells can then be cloned, and the clones can be screened for the production of antibody against the antigen(s) used initially for immunization. Selected hybridomas can then be grown in cell culture to produce monoclonal antibodies, implanted in animals to obtain ascites or serum rich in monoclonal antibodies or frozen as a permanent source of specific antibody-producing cells.

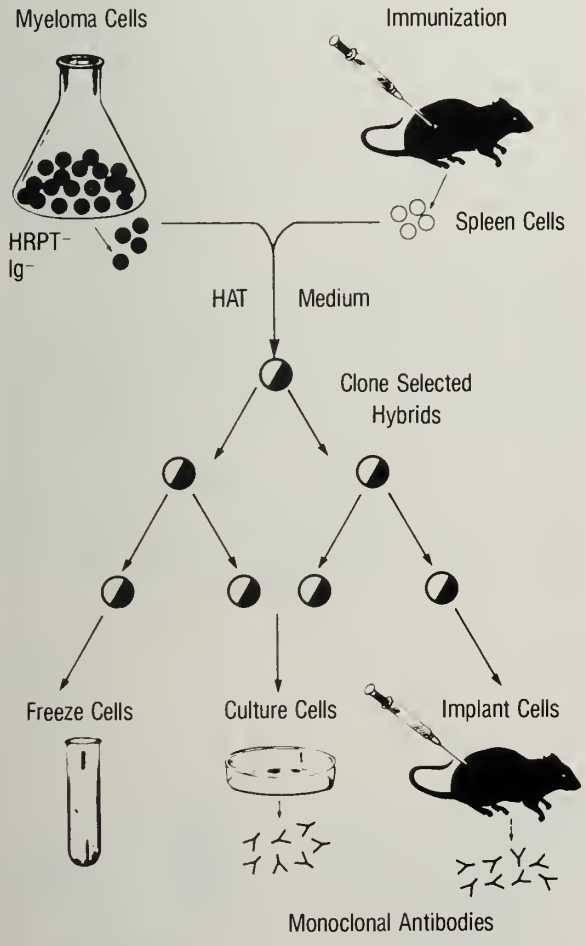

Figure 1.—Schematic representation of the steps involved in producing monoclonal antibodies. Lymphocytes are incubated with myeloma cells in the presence of an agent that facilitates fusion of cell membranes. The incubation is conducted in selection (HAT) medium that supports the growth of lymphocyte/myeloma fusions (◑) only. Individual hybrid cells are then cloned and screened for producing desired monoclonal antibodies. Selected clones ("hybridomas") can then be (1) frozen as a permanent source of specific antibody-producing cells, (2) grown in cell culture to produce monoclonal antibodies or (3) implanted in experimental animals to produce high concentrations of monoclonal antibodies that can be purified from ascites or serum. HPRT⁻ = hypoxanthine phosphoribosyl transferase-negative, Ig⁻ = immunoglobulin-negative

Advantages of Monoclonal Antibodies

Conventional antiserums are heterogeneous reagents composed of many structurally and functionally distinct antibody molecules that react with many different antigenic determinants. They are not reproducible reagents, but rather vary in their composition depending on their source and the particular point in time when they are obtained. In contrast, monoclonal antibodies are homogeneous, reproducible reagents that can be characterized precisely and that have a highly restricted pattern of reactivity.

The most important advantage of monoclonal antibodies over conventional antiserum is the ability to produce pure antibody without a pure antigen. That is, it is possible to use a preparation containing many different antigens—such as a suspension of lymphocytes—to produce a panel of monoclonal antibodies, each of which will react with one and only one antigenic determinant (Figure 2). As a result, it is possible to generate monoclonal antibodies that will identify subsets of cells that might otherwise be difficult to distinguish, such as helper or suppressor T cells, pathogenic or nonpathogenic organisms, benign or malignant cells. The great promise for the use of monoclonal antibodies in the treatment of cancer or autoimmune disease largely reflects this characteristic.

Antibodies to Major Histocompatibility Antigens

The first attempts to use monoclonal antibodies to alter the course of autoimmune disease involved antibodies directed against major histocompatibility antigens.[3-5] This strategy was based on the fact that many autoimmune diseases are associated with particular human leukocyte antigens: HLA-DR. These antigens, also called class II major histocompatibility antigens (MHA II), play an important role in promoting immune responses, as shown in Figure 3. The response of helper T cells to antigen and the subsequent development of humoral and cellular immunity require that antigen be presented to T cells in association with MHA II on antigen-presenting cells. Because of this critical role in the immune response, MHA II (HLA-DR) antigens are often referred to as immune-associated (Ia) antigens.

McDevitt and colleagues reasoned that because MHA II is required to promote immunity and because certain MHA II antigens are associated with autoimmunity, it might be possible to retard autoimmunity by administering monoclonal antibodies to appropriate MHA II antigens.[3] This hypothesis has been tested and supported in animal models for multiple sclerosis,[3] myasthenia gravis[4] and systemic lupus erythematosus.[5] For example, in several animal species, immunization with myelin basic protein causes a demyelinating disease of the central nervous system that resembles multiple sclerosis.

This disease, called experimental allergic encephalitis, can be prevented in mice by administering monoclonal antibodies to MHA II before immunizing.[3] When treatment is initiated after immunization, the disease is delayed but not prevented. Monoclonal antibodies to MHA II have also been used successfully in mice with experimentally induced myasthenia gravis.[4] Treatment with monoclonal antibodies to MHA II at the time of immunization with acetylcholine receptor not only attenuates both humoral and cellular immune responses to the acetylcholine receptor, but also significantly reduces the frequency and intensity of the clinical manifestations of experimentally induced myasthenia gravis.

Monoclonal antibody to MHA II has been effective not only in autoimmune diseases induced by immunizing with antigen, but also in the spontaneous autoimmune disease of the F1 hybrid of New Zealand black and New Zealand white (B/W) mice.[5] Antibodies to double-stranded DNA spontaneously develop in B/W mice and the mice die of immune-complex glomerulonephritis. Female B/W mice are more severely affected than males, and the immunologic abnormalities that occur in these mice closely parallel the immunologic abnormalities in people with systemic lupus erythematosus.[6] Adelman and co-workers[5] treated female B/W mice with weekly injections of monoclonal antibodies to MHA II beginning at age 4 months before the onset of overt autoimmune disease. Such treatment substantially reduced renal disease and increased the one-year survival rate from 10% in control mice to greater than 90% in treated mice.

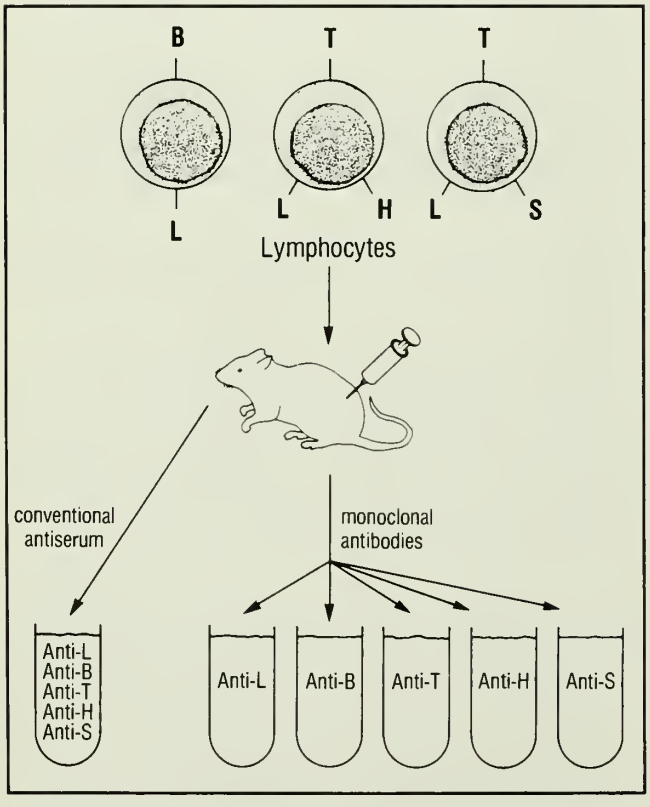

Figure 2.—Production of antilymphocyte antibodies. Lymphocytes express many different antigens. Some antigens are common to all lymphocytes **(L)**; some are restricted to B cells **(B)** or T cells **(T)**; some are unique to helper **(H)** or suppressor **(S)** T cells. Conventional antilymphocyte serum consists of a heterogeneous mixture of antibodies to all of these antigens. In contrast, monoclonal antilymphocyte antibodies are pure reagents that react with specific antigens. Therefore, unlike conventional antiserum, they can be used to identify specific lymphocyte subsets, to characterize immune defects—such as helper T-cell deficiency in acquired immunodeficiency syndrome—and to focus immunosuppressive therapy on selected cell subsets.

Although it is possible that the beneficial effects of monoclonal antibody to MHA II reflect its ability to block the interaction between antigen-presenting cells and helper T cells (see Figure 3), such treatment may influence other cells as well. In mice, MHA II is expressed on B cells and activated T cells in addition to macrophages. Recent studies indicate that treatment with antibodies to MHA II removes B cells from the spleen and lymph nodes,[7] suggesting that B-cell depletion may contribute to the immunosuppressive effects of monoclonal antibodies to MHA II. In higher mammals, MHA II is expressed on vascular endothelium[8] and, in people with autoimmune diseases, it may also be induced on the cells of target organs.[9] This widespread expression of MHA II may prove to be a significant barrier to the use of monoclonal antibodies to MHA II in humans.

MHA II-dependent T-cell responses can be blocked in vitro not only by monoclonal antibodies to MHA II, but also by monoclonal antibodies to the T-cell antigens that interact with MHA II on antigen-presenting cells.[10-12] As discussed in the next section, these anti-T cell antibodies provide an alternative approach to treatment that may be more selective in its effect on the immune system than monoclonal antibodies to MHA II.

Antibodies to T-Cell Antigens

Many T-cell antigens have been considered as possible targets for immunosuppressive therapy with monoclonal antibodies. This strategy reflects the functional importance of T cells in the development of immunity. It is supported by previous studies showing that antithymocyte serum causes immune suppression. Monoclonal antibodies to antigens expressed on all T cells are currently being investigated in patients with multiple sclerosis.[13] Anti-T cell antibodies have already been used to reduce autoimmunity in a unique murine model for systemic lupus erythematosus (MRL/*lpr*) that is

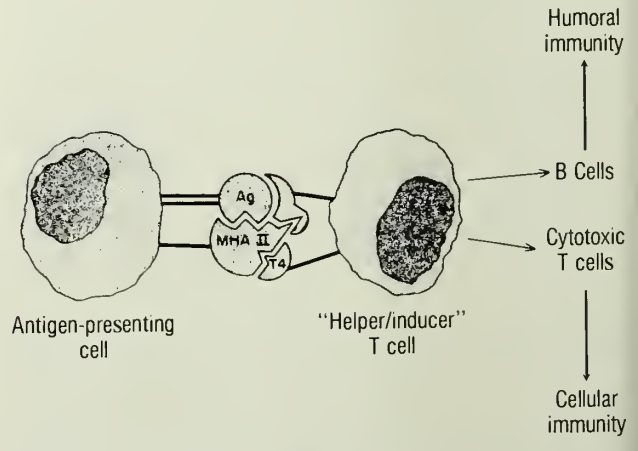

Figure 3.—The response of helper T cells to antigen (Ag), and the subsequent development of humoral and cellular immunity, requires T-cell recognition of both antigen and class II major histocompatibility antigens (MHA II) on antigen-presenting cells. This response involves a T-cell receptor that recognizes antigen in association with MHA II. It is facilitated by another molecule on T cells (T4 in humans) that binds to MHA II.

caused by massive proliferation of T cells.[14] However, monoclonal antibodies to pan-T cell antigens may also have undesirable effects because these antibodies may interfere with the function of all T-cell subsets. Therefore, alternative strategies are being developed to focus therapy more specifically on the T-cell subsets (or antigens) that contribute to autoimmunity.

Mature T cells can be divided into two major subsets.[15,16] In humans, these subsets can be distinguished by the expression of either the T4 antigen or the T8 antigen (Figure 4). The subset expressing T4 is often referred to as the "helper/inducer" subset because it is composed primarily of cells that promote immunity. The subset expressing T8 is often referred to as the "suppressor/cytotoxic" subset because it is composed primarily of cells that suppress immunity or mediate cytotoxicity. These T-cell subsets can be defined more precisely by the distinct mechanisms through which they interact with antigen-presenting cells. Cells expressing T4 recognize antigen in association with class II major histocompatibility antigens, such as HLA-DR, on antigen-presenting cells (see Figure 3), whereas cells expressing T8 recognize antigens in association with class I major histocompatibility antigens, such as HLA-A, HLA-B and HLA-C, on antigen-presenting cells. The T4 and T8 molecules apparently bind to MHA II and MHA I, respectively, thereby facilitating the distinct functional responses of the two major T-cell subsets. Consequently, monoclonal antibodies to T4 can be used in vitro to block the function of $T4^+$ cells, and antibodies to T8 can be used in vitro to block the function of $T8^+$ cells.[10]

Because the T4 molecule plays an important role in stimulating T-cell responses that promote immunity, it has been suggested that monoclonal antibodies to T4 might inhibit T-cell responses that contribute to autoimmunity. This hypothesis has been tested in autoimmune mice, using antibodies to the mouse T-cell antigen that is structurally and functionally homologous to T4 in humans. This mouse antigen is called L3T4 to emphasize its homology with the human antigen designated Leu-3 or T4.[17] Several studies indicate that monoclonal antibody to L3T4 profoundly suppresses autoimmunity in mice.[18-20] For example, treatment of lupus-prone B/W mice with weekly injections of rat monoclonal antibody to L3T4 from age 4 to 12 months prevented spontaneous autoimmunity.[18] In control B/W mice treated with either saline or nonimmune rat immunoglobulin (Ig)G, high titers of antibody to double-stranded DNA developed, whereas in mice treated with monoclonal antibodies to L3T4, few, if any, anti-DNA antibodies developed (Figure 5). Antibodies to L3T4 also significantly reduced renal disease. Most importantly, treatment with monoclonal antibodies to L3T4 dramatically prolonged life (Figure 6). Median survival was 9.3 months in mice treated with saline and 7.6 months in mice treated with nonimmune rat IgG. In contrast, all of the mice treated with anti-L3T4 lived at least 10 months, and 80% were still alive

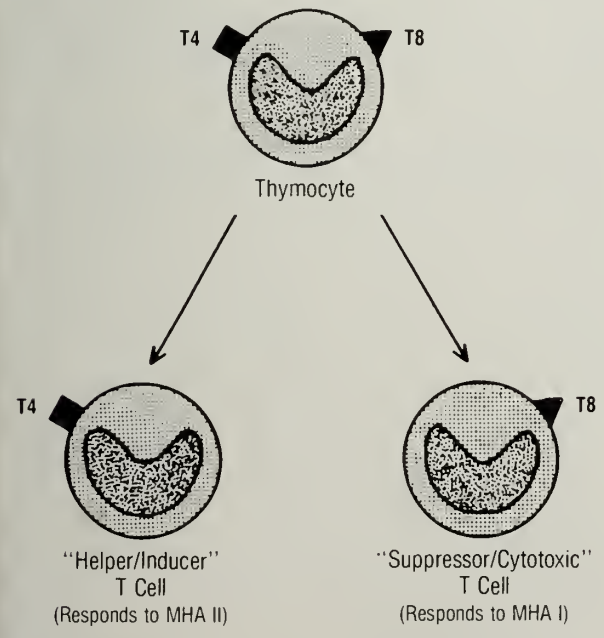

Figure 4.—Immature thymocytes, expressing both T4 and T8, differentiate into mature T cells that express either T4 or T8. $T4^+$ cells, often referred to as "helper/inducer" T cells, respond to antigen in association with class II major histocompatibility antigens (MHA II) on antigen-presenting cells. $T8^+$ cells, often referred to as "suppressor/cytotoxic" T cells, respond to antigen in association with class I major histocompatibility antigens (MHA I) on antigen-presenting cells.

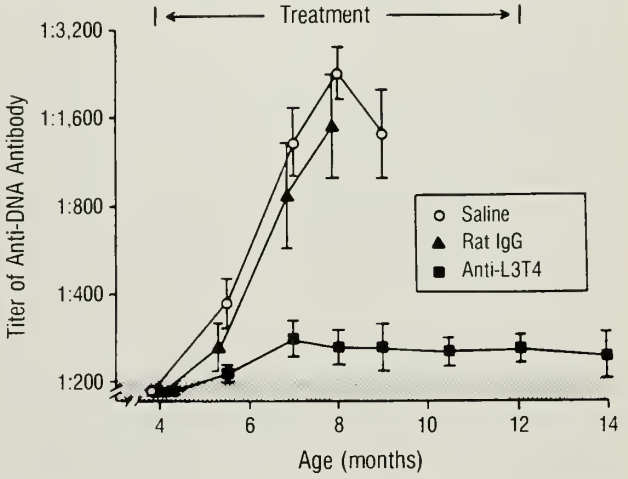

Figure 5.—Geometric mean titer (× standard error of the mean) of antibody to double-stranded DNA in hybridized New Zealand black and New Zealand white mice treated with weekly injections of saline (○), nonimmune rat IgG (▲) or monoclonal anti-L3T4 (■). The shaded area indicates the titer of anti-DNA antibody (<1:200) in normal (C57BL/6) mice.

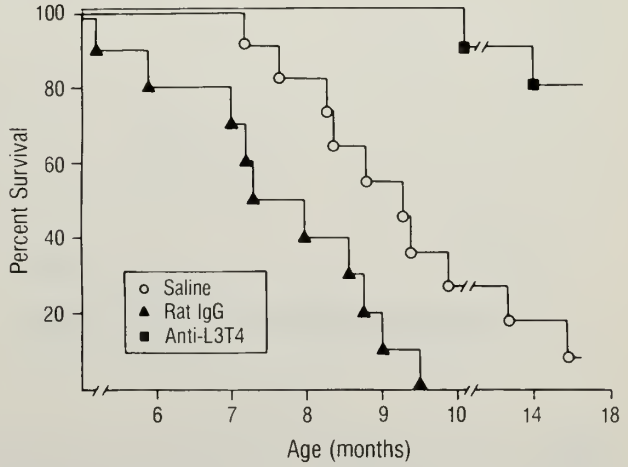

Figure 6.—Survival in hybridized New Zealand black and New Zealand white mice treated with weekly injections of saline (○), nonimmune rat IgG (▲) or monoclonal anti-L3T4 (■) from age 4 months to age 12 months.

at age 18 months. These observations establish that helper T cells play an important role in the pathogenesis of autoimmune disease in B/W mice. Moreover, they show that monoclonal antibodies to L3T4 can significantly retard the development of lupus in these mice. Similar findings have been reported recently in another, genetically unrelated, murine model for systemic lupus erythematosus.[21] It should be emphasized, however, that in the studies of murine lupus reported thus far, treatment with antibodies to L3T4 was initiated before the onset of clinically overt autoimmune disease. Studies are currently in progress to determine whether monoclonal antibodies to L3T4 can be used not only to prevent murine lupus, but also to reverse established disease.

Monoclonal antibody to L3T4 has also been used successfully to prevent two experimentally induced autoimmune diseases in mice. Ranges and associates prevented collagen-induced arthritis by repeated administration of monoclonal antibodies to L3T4 beginning at the time of immunization with type II collagen.[20] Similarly, Waldor and colleagues[19] prevented experimental allergic encephalitis in mice by administering monoclonal antibody to L3T4 at the time of immunization with a mouse spinal cord homogenate containing myelin basic protein. The capacity of anti-L3T4 to reverse experimental allergic encephalitis was also investigated. When treatment with monoclonal antibody to L3T4 was initiated at the first sign of paralysis, clinical abnormalities resolved and subsequent progressive neurologic disease was prevented in 90% of cases. However, when antibody to L3T4 was withheld until severe neurologic deficits were present, treatment was ineffective.

The beneficial effects of monoclonal antibody to L3T4 clearly are not limited to a particular strain of mice or to a particular disease. These effects have been shown in two murine models for systemic lupus erythematosus[18,21] and in murine models for rheumatoid arthritis[20] and multiple sclerosis,[19] suggesting a broad range of potential clinical applications for antibody to L3T4 and its human homologue, T4. For example, based on the effects of monoclonal antibody to L3T4 in experimental allergic encephalitis, preliminary trials are now being initiated to examine the effects of antibody to T4 in patients with multiple sclerosis.

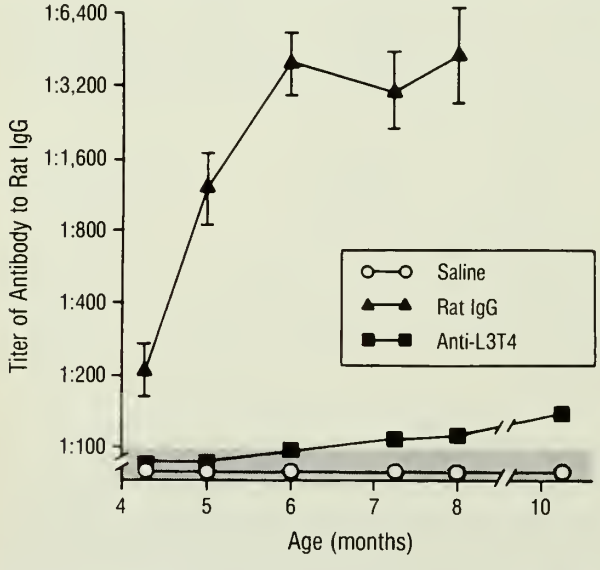

Figure 7.—Geometric mean titer (± standard error of the mean) of antibodies to rat immunoglobulin in hybridized New Zealand black and New Zealand white mice treated with weekly injections of saline (○), nonimmune rat IgG (▲) or monoclonal anti-L3T4 (■) beginning at age 4 months. The shaded area indicates assay results using normal mouse serum as negative controls.

One of the main obstacles to the successful use of either conventional antiserum or monoclonal antibody as therapeutic agents has been the development of host immunity to the administered immunoglobulin.[22,23] This problem does not occur in mice treated with rat antibody to L3T4,[18] apparently reflecting the capacity of this antibody to block helper T-cell function and thereby block the host immune response to the monoclonal antibody (Figure 7). In contrast, mice treated with other rat antibodies or with nonimmune rat IgG produce high titers of antibody to rat immunoglobulin. These antibodies can cause serum sickness that accelerates mortality (Figure 6),[18] and they can even cause anaphylaxis.[14] Thus, treatment with monoclonal antibody to L3T4 not only retards autoimmune disease, but also prevents the development of a potentially harmful host immune response to therapy.

Recent studies indicate that total lymphoid irradiation may reduce the severity of intractable rheumatoid arthritis[24] and lupus nephritis.[25] This may work by causing prolonged depletion and impaired function of $T4^+$ cells.[24] Monoclonal antibody to T4 provides an alternative method of depleting $T4^+$ cells that may be safer and better tolerated than total lymphoid irradiation.

The therapeutic value of monoclonal antibody to T4 may depend largely on the extent to which treatment adversely affects normal immune function. Studies in our laboratory and elsewhere indicate that treatment with monoclonal antibody to L3T4 profoundly suppresses humoral immunity and, to a lesser extent, also suppresses cellular immunity.[26-28] Preliminary studies indicate that these effects are reversible. Nonetheless, it remains to be determined whether the beneficial effects of anti-L3T4 on autoimmunity can be achieved without producing unacceptably severe suppression of normal immune function.

Another new approach to the treatment of autoimmune disease involves monoclonal antibody to antigens that are expressed on activated T cells. When T cells are stimulated, they express certain antigens that are not present on resting T cells. In several autoimmune diseases, there is an increase in the frequency of activated T cells, and these cells may contribute to the development of autoimmune disease.[29,30] It may be possible, therefore, to use monoclonal antibody to antigens on activated T cells to selectively deplete these cells and thereby favorably influence the course of autoimmune disease. In multiple sclerosis, for example, the number of activated T cells is increased in the blood and in the spinal fluid.[30] The presence of these cells correlates with disease activity, supporting the hypothesis that they may be involved in the pathogenesis of the disease. Preliminary studies have been initiated to determine whether monoclonal antibody to specific T-cell activation antigens will be effective in patients with multiple sclerosis.[13]

Antibodies to Autoantibodies

A more selective approach to the treatment of autoimmunity involves the use of monoclonal antibodies to unique determinants on autoantibodies.[31] This approach is based on the

fact that T cells and B cells have surface receptors for the antigens with which they react. The antigen receptor on B cells is the antibody molecule itself. This molecule consists of constant regions that are shared by many other antibodies and variable regions that include unique determinants, called "idiotypes." These idiotypes reflect the unique structure of an antibody that allows it to react with a specific antigen. Different B cells that react with the same antigen may express shared ("cross-reactive") idiotypes. Consequently, it may be possible to use monoclonal antibody directed against cross-reactive idiotypes on autoantibodies to focus therapy on different cells that recognize the same autoantigen. This hypothesis has been supported by studies in which anti-idiotype antibody to anti-DNA was used successfully to suppress lupus nephritis in B/W mice.[31] In these studies, however, the beneficial effect of anti-idiotype monoclonal antibody was transient because of the appearance of anti-DNA antibodies lacking the idiotype. Current work in this area is focused on the characterization of cross-reactive idiotypes among autoantibodies, with the hope that more broadly cross-reactive idiotypes can be identified.[32,33]

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Monoclonal Antibodies—Therapeutic and Diagnostic Uses in Malignancy

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Murine monoclonal antibodies represent an attractive type of antitumor therapy because of their potential for exquisite specificity, production in large, pure quantities and mediation of in vivo cytotoxic effects. With maturing monoclonal antibody technology has come the use of these antibodies in clinical studies in patients with malignancy. These trials have established that monoclonal antibodies can be safely administered in large doses, that their pharmacokinetics and tissue penetration can be predicted and that in some instances a therapeutic effect can be produced by their infusion. A number of problems have also been identified by these studies, including antigenic heterogeneity of the tumor, the presence of free serum antigen, the immunogenicity of the xenogeneic antibody, modulation of the surface antigen by the antibody and a finite capacity of human effector mechanisms to mediate cytotoxicity directed by murine antibodies. Other workers are concurrently investigating the use of monoclonal antibodies in the ex vivo elimination of cells from bone marrow, as probes for serum tumor marker antigens and as carriers for radioimaging agents or toxins. Although most of these endeavors are at the earliest stages, promising preliminary results presage an important role for native and altered monoclonal antibodies in the diagnosis and treatment of malignant conditions.

(Lowder JN, Levy R: Monoclonal antibodies—Therapeutic and diagnostic uses in malignancy, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:810-818)

In 1906 Paul Ehrlich initially proposed the concept of an antiserum not only specific for a tumor but which after binding to it would mediate its regression.[1] Since that time the search for antiserum fulfilling both these criteria has met with little success in humans. Antiserum obtained from the blood of an immunized animal is heterogeneous, variable from lot to lot and requires extensive absorption with consequent loss of activity to produce specificity. The development of hybridoma technology by Kohler and Milstein in 1975 alleviated these problems.[2] With this technique, lymphocytes from the spleen of a mouse appropriately immunized can be immortalized by fusing them to myeloma cells that have lost the ability to make their own immunoglobulin but are capable of unlimited mitotic division.[3] Through limiting dilution, individual lymphocyte-myeloma hybrids, which produce an antibody of unique specificity, avidity and effector function, can be isolated or cloned from the many hybrids resulting from such a fusion. A cloned hybrid cell line can theoretically produce unlimited quantities of a single antibody of specific and well-characterized binding specificity, avidity and isotype. The capabilities exist to select and produce an antibody fulfilling whatever criteria are deemed important to its purpose. The quantities necessary for therapy in humans or other large-scale application are usually prepared from mouse ascites. These ascites preparations contain varying amounts of mouse albumin, transferrin and nonspecific immunoglobulin after purification. Eliminating contamination by murine viruses, which are potentially pathogenic in humans, is a legitimate concern in ascites-derived antibodies.[4] In vitro methods currently available, however, make the production of gram quantities of monoclonal antibodies of very high purity a practical reality.[5] Because of the monoclonality of the immunoglobulin, no absorption is necessary and virtually all of the antibody in the preparation can be recovered for use. Thus, the production of large quantities of a pharmaceutically pure, highly specific monoclonal antibody is not only a theoretic but a practical reality.

The clinical potential for these reagents in oncology exceeds that of Ehrlich's theoretic antitumor antiserum. As diagnostic reagents, they may help monitor therapy or detect

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ABBREVIATIONS USED IN TEXT

ADCC = antibody-dependent cellular cytotoxicity
AMIA = antimouse immunoglobulin antibody
CALLA = common acute lymphoblastic leukemia antigen
Ig = immunoglobulin

occult disease. The monoclonal antibodies could be used to detect minute amounts of free tumor-associated antigens in the serum, antigen-positive cells in the blood or tissue biopsy specimen or as in vivo imaging reagents in the form of immunoconjugates. Their specificity could be used to localize conjugated toxic agents to the tumor, thus producing a response. These issues, both realized and potential, are discussed in this article.

Monoclonal Antibody Therapy in Patients With Malignancy

General Considerations of In Vivo Administration

Monoclonal antibodies specific for various malignant conditions are currently being investigated as therapeutic agents in many centers around the United States. Unlike conventional therapy, which can be tested for activity against a variety of malignant tumors, monoclonal antibodies have a predefined potential activity limited to tumors bearing their target antigen on their surface. Whatever the mechanism of an antibody-induced clinical response, we presume that it must result from binding of antibody to the surface of all of the cells in the tumor with proliferative capacity.

The ideal target for a monoclonal antibody would be an antigen expressed in high density on the surface of only tumor cells, that is not secreted or shed as free protein and that does not modulate (see Table 1). This antigen must be on the surface of every tumor cell, especially any stem cell population that exists, and have no capacity for structural change that might alter its reactivity with the antibody. The targets of most antibodies used in therapeutic trials to date are tumor-associated differentiation antigens that are also expressed on certain normal cells, usually in lower density. A search continues for fetal proteins or oncogene expression products on the cell surface of malignant tumors that might be used as discriminating targets.

Tumor Heterogeneity

Subpopulations of the tumor may express a mutated form of the antigen or lack the surface antigen altogether, thus rendering them unreactive with the antibody.[6] Selection of drug-resistant subsets of tumor is a well-known mechanism of escape from chemotherapy. It is only logical that if an effective negative selection force—in this case, monoclonal antibodies—exists, then cells unreactive with the antibody would have a growth advantage and emerge as the predominant population. This phenomenon was noted by Meeker and coworkers in two patients with B-cell lymphoma treated with anti-idiotype antibodies.[7] No unreactive cells were detected before therapy with a single antibody, suggesting that the variants were present at a frequency of less than 1 in 200, the lower limit of detection sensitivity. In this instance, a minor mutation occurred in the expressed surface immunoglobulin, making it unreactive with the anti-idiotype antibody but otherwise similar to the initial idiotypic immunoglobulin. Other

TABLE 1.—*Problems With the In Vivo Use of Monoclonal Antibodies*

Specificity of antibody: tumor-associated versus tumor-specific antigens
Antigenic heterogeneity of the tumor cell population
Extracellular free antigen
Immunogenicity of the mouse immunoglobulin
Modulation
Antibody-host ability to mediate directed cytotoxicity
Nonspecific (Fc-mediated) localization of antibody

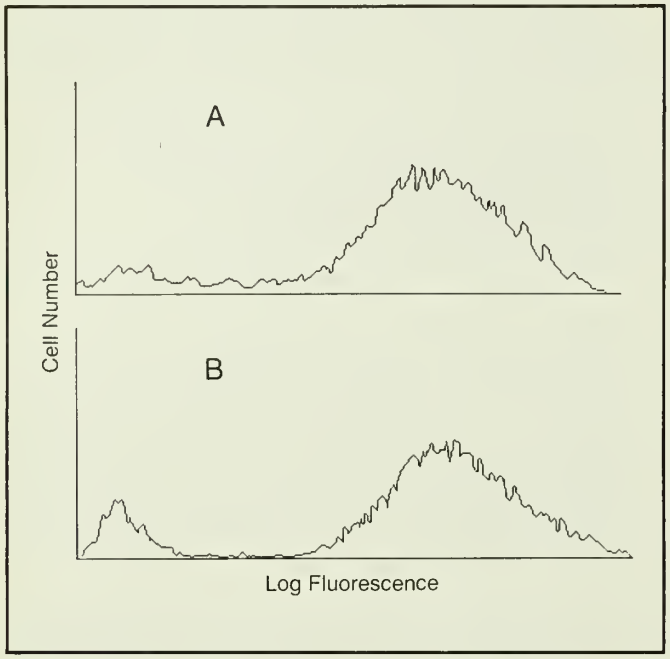
situations that might result in a loss of antibody reactivity include mutations causing an inability to translate the target protein gene, glycosylate or express on the cell surface cytoplasmic protein and the antibody-mediated reversible loss of surface antigen—modulation—discussed below (Figure 1). Other clinical studies in humans have shown measurable subpopulations unreactive with the therapeutic antibody, but none have identified this as a mechanism of escape of tumor from an antibody-induced regression of disease.

Free Antigen

The presence of a large quantity of free antigen in the serum represents a serious impediment to treatment with monoclonal antibodies specific for that antigen. This free antigen would be as likely to bind infused antibody as cell surface antigen and by forming complexes would consume antibody and block penetration and binding of antibody to extravascular tumor. The formation of large amounts of immune complexes might also produce toxicity. Free antigen was noted to be a practical problem in the study by Nadler and associates.[8] The treatment of lymphoma with anti-idiotype was also complicated by the presence of circulating free idiotype protein.[9] Small amounts of free antigen have been detected transiently in other studies but none have proved significant to monoclonal antibody therapy.[10,11]

Immunogenicity

Control of the host response against the xenogeneic antibody is important to the ultimate success of monoclonal antibody therapy. Not only do the antimouse immunoglobulin antibodies (AMIA) consume antibody and prevent its binding to cellular target antigen, but attendant toxicity prohibits infusing large quantities of antibody.[9] The incidence of AMIA varied in different studies, depending on the immunocompetence of the subjects. AMIA is first detectable between 7 and 30 days after the initial dose of antibody. It reacts with both the constant region of the antibody and its variable region (idiotype).[9,12-14] As patients with less advanced disease are treated, their immune systems might be expected to be more competent and the likelihood of AMIA developing may be greater. The use of concurrent therapies to suppress the response or produce immunologic tolerance has shown some effects but is not yet practical.[12] The initial administration of large doses of highly purified monoclonal antibodies may induce "high zone tolerance," a suppression of the antibody response by very large doses of antigen.[15] The development of less immunogenic human monoclonal antibodies or recombinant chimeric antibodies might minimize the importance of this problem, if anti-idiotype antibodies are not produced.[16,17]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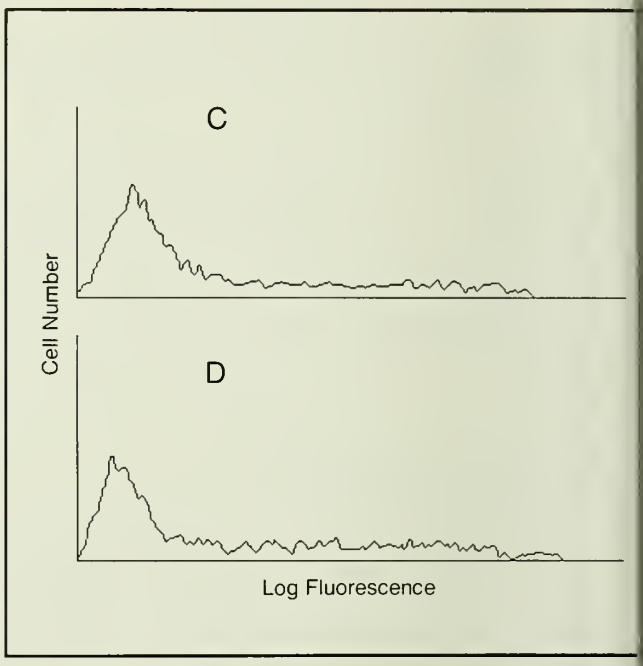
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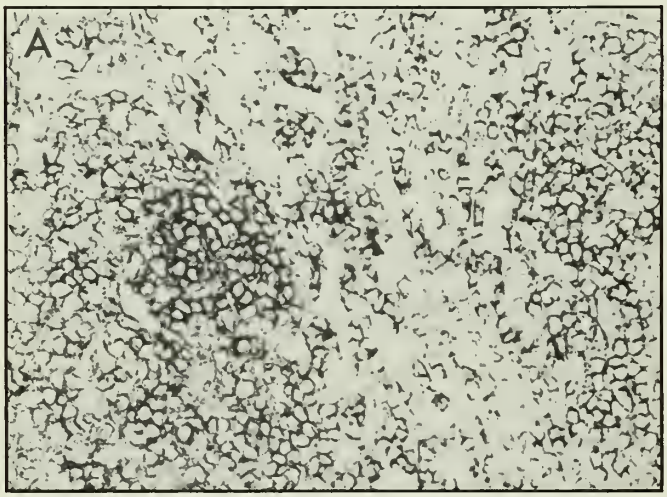
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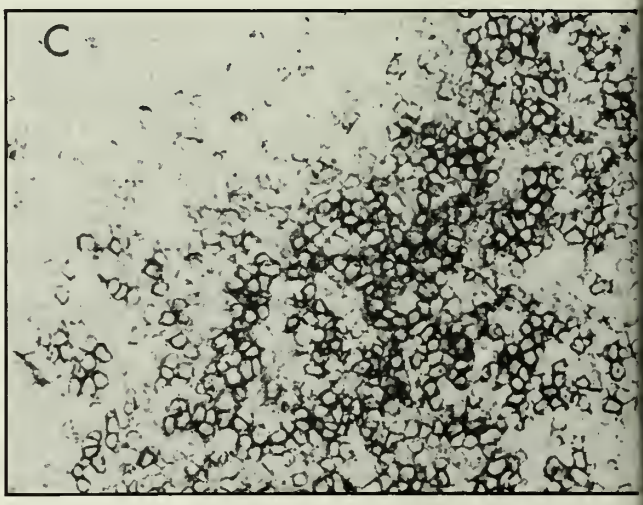
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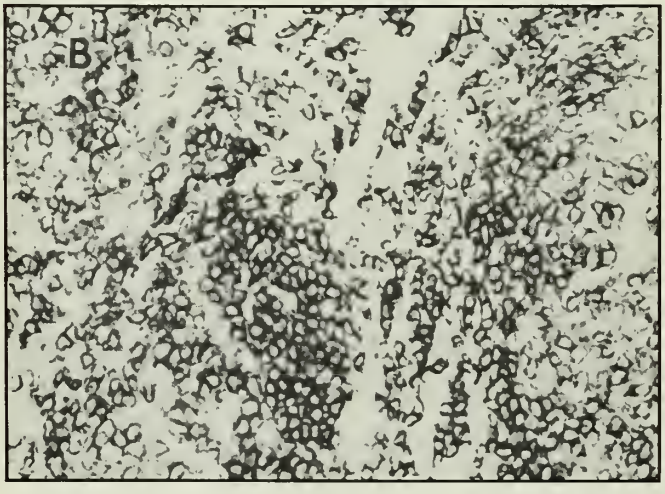
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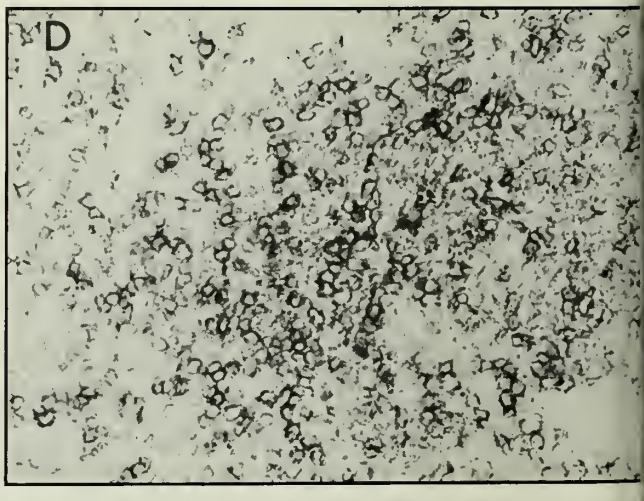
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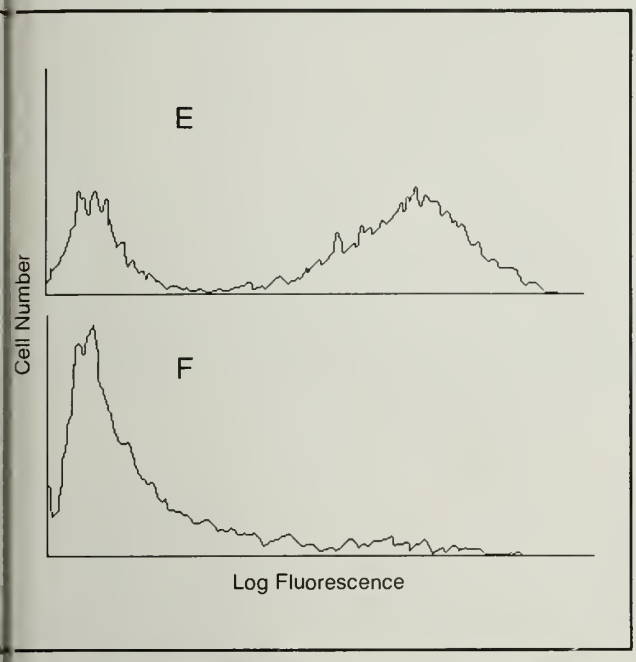

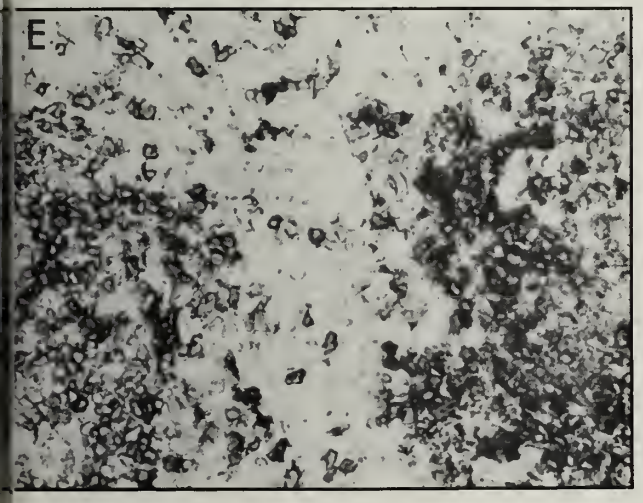

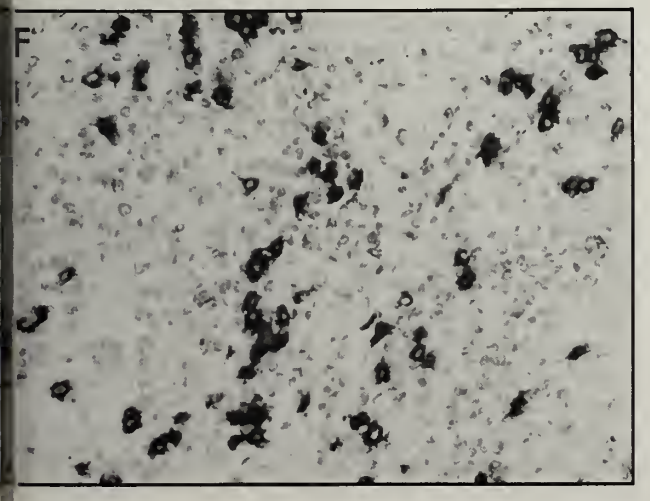

Figure 1.—Comparison of flow cytometry fluorescence histograms of single-cell suspensions with immunoperoxidase staining of frozen tissue sections. These represent the two most commonly used methods of assessing antibody reactivity with cellular antigens. **A** (anti-μ) and **B** (anti-idiotype) represent staining with two antibodies specific for different epitopes of the surface immunoglobulin of a B-cell lymphoma before treatment with anti-idiotype antibody. A gaussian distribution of each cell population is seen in the fluorescence histograms, the brightest staining—or "positive"—cells on the right of each curve, the dullest staining—"negative"—on the left. The frozen sections are stained with the appropriate mouse antibody and then detected with an antimouse immunoglobulin (Ig) avidin-biotin peroxidase method. The dark precipitate identifies cells that bind the antibody of interest. The staining patterns using both methods are the same for both antibodies before therapy. **C** (anti-μ) and **D** (anti-idiotype) represent staining 18 hours after a large dose of anti-idiotype antibody. The fluorescence histograms show a greatly decreased number of positive cells for both antibodies. This is caused by *modulation,* antibody-mediated internalization of the surface immunoglobulin. The tissue sections show continued reactivity with both anti-μ and anti-idiotype antibody, perhaps because this method detects both surface and cytoplasmic immunoglobulin. Thus, modulation is better assessed with flow cytometry than with tissue sections. Discordance of reactivity with the two antibodies is seen in a posttherapy tumor specimen (panels **E** [anti-μ] and **F** [anti-idiotype]). Although both surface and cytoplasmic IgM are detectable, only a minor population of tumor cells reacts with the anti-idiotype antibody. This is consistent with heterogeneity of the tumor cells that developed after selection of an antigen-negative subpopulation by the anti-idiotype therapy. (All photomicrographs are original magnification × 350, courtesy of Carlos Garcia and Roger Warnke.)

Modulation

Modulation is the term that describes the coalescence of surface antigen cross-linked by multivalent antibody followed by internalization of the complex.[18] This renders the modulated cell surface antigen-negative and, thus, resistant to serotherapy by antibodies against that antigen.[19] On the other hand, if the antibody is conjugated to a toxin, internalization of the antigen-antibody complex may potentiate the effects of the "armed" antibody. Modulation of one surface antigen does not appear to affect other cell surface proteins and the malignant cells can still be identified using other specific surface antigens. Once antibody is not present, the modulated antigen will be reexpressed. In general, antigens on the surface of lymphoid cells are more easily modulated than those on solid tumors.

Toxicity

Intravenous monoclonal antibody infusions are frequently associated with toxicity that is tolerable in most cases and with careful attention can be minimized. Virtually all studies agree that the amount of toxicity depends on the amount of intravascular target antigen, whether it is in the form of free antigen, antigen-bearing cells or AMIA.[9,20,21] This suggests that immune complexes or cellular immunoaggregates produce the toxic effects, although this has not been proved. Idiosyncratic anaphylactoid reactions are rare and have never been described in the absence of an intravascular target. Local reactions to intradermal injection or a scratch test with the monoclonal antibody failed to predict systemic reactions. Pretreatment with acetaminophen and diphenhydramine hydrochloride mitigates the symptoms associated with reactions. The most common symptoms include chills, fever, hyperemia of the conjunctivae and mucous membranes, urticaria, periorbital edema, dyspnea, wheezing, hypotension, nausea and emesis (Table 2). Interrupting the antibody infusion is the most useful measure to control these symptoms when they occur. Parenteral administration of diphenhydramine, meperidine hydrochloride (for rigors) and prochlorperazine is useful to alleviate specific problems. In some studies 24-hour infusions were used to limit toxicity that appears to be infusion-rate dependent. These symptoms seem to occur at an equivalence point, and when the infused antibody is in excess in the serum, the infusion may proceed without side effects. Toxic reactions seldom prevent the infusion of even large doses of monoclonal antibody. The most severe reported toxicity was associated with infusion of large doses of antibody in the presence of established AMIA.[9]

Host Immune System and Mechanism of Response

The finite capacity of the host-effector mechanisms that are directed by the antibody to produce cytotoxicity may ultimately be the major limitation to therapy for malignant tumors with native murine monoclonal antibodies. The proposed mechanism of antitumor effect in human trials is based on results in studies using animals, primarily mice.[22] The destruction of an antibody-coated cell in vitro is mediated either by complement (cell-mediated cytotoxicity) or Fc receptor-bearing cells (antibody-dependent cellular cytotoxicity [ADCC]). Studies of ADCC with murine antibodies and human effector cells suggest that immunoglobulin (Ig)[23,24] G2a and IgG3 are the most effective murine heavy chain isotypes. Human complement fixation is best achieved by IgM and IgG3.[25] However, treatment with an antibody active in vitro does not guarantee success in vivo. Circulating cells binding antibody of any mouse heavy chain subclass are cleared from the blood by the reticuloendothelial system. Unless sustained, this decrement in circulating cells does not constitute a clinical response nor does it predict a response in other sites. Other possible mechanisms through which a native antibody-mediated tumor response might occur are an antiproliferative effect (anti-Ig, anti-DR, G5) or blocking the binding of a substance necessary to support the growth of the cell (antiepidermal growth factor, antitransferrin receptor, anti-B cell growth factor).[26-31]

TABLE 2.—*Toxicity of Monoclonal Antibody Infusions*

Toxic Effect	*Frequency (%)*
Chills	0 to 63
Fever	0 to 63
Pruritus, urticaria	5 to 80
Dyspnea, wheezing	0 to 30
Nausea, vomiting, diarrhea	0 to 30
Hypotension	0 to 10
Facial edema	0 to 20
Serum sickness	rare*
"Anaphylactoid reaction"	rare
Facial palsy	rare

*Observed only after infusion of monoclonal antibody during active antimouse immunoglobulin antibody response.

Clinical Trials

Malignant Hematolymphoid Disorders

Most of the clinical trials with monoclonal antitumor antibodies have been done in patients with leukemia or lymphoma. The accessibility of tumor cells in the blood allows convenient assessment of both antibody binding and response to therapy. Large numbers of antibodies have been developed against normal and malignant lymphoid cells. The monoclonal antibodies used in these trials have represented both extremes in specificity, from differentiation antigens present on normal cells, such as the T65 antigen, to antibodies specific for a unique tumor in a single patient, or anti-idiotype antibodies.[9,10,20,21,32,33] The results of these trials are summarized in Table 3.

T101 and anti-Leu-1 antibodies are specific for the T65 antigen present on both malignant and normal T cells and a subset of normal and malignant B cells. These antibodies were used to treat patients who have cutaneous T-cell lymphoma and chronic lymphocytic leukemia, a B-cell malignant disorder in which the T65 antigen is expressed.[10,20,21,32,33] These patients were refractory to conventional therapy. Infusion of either antibody led to the elimination of circulating antigen-positive cells from the blood. This elimination of cells was usually transient, the tumor cells reappearing in the blood within 24 hours. Doses of antibody, all delivered intravenously, varied from 1 to 600 mg. With increasing doses of antibody, saturation of the antigen on circulating cells was achieved and free antibody was ultimately detectable in the serum. Once the cells in the blood were saturated and antibody excess was achieved, modulation of surface antigen occurred and antigen-negative tumor cells could be identified in the blood. When free antibody was no longer detectable in the serum, surface antigen-bearing cells were again present in

TABLE 3.—*Clinical Trials With Monoclonal Antibodies Specific for Hematolymphoid Malignancy*

Institution	Disease	Monoclonal Antibody	Dose (mg)	AMIA*	Tumor Response†	Sources
Dana-Farber‡	Lymphoma	AB89	25 to 150	0	0	Nadler et al, 1980[8]
Dana-Farber	ALL	J5	1 to 175	ND	0	Ritz et al, 1981[19]
UC San Diego§	CLL	T101	10 to 500	0/6	0/6	Dillman et al, 1984[32]
NCI‖	CLL	T101	1 to 100	0/13	0/13	Foon et al, 1984[20]
Stanford¶	CTCL	Leu 1	1 to 600	6/13	8/13	Miller et al, 1983[10]
UC San Diego	CTCL	T101	10 to 500	3/10	5/10	Dillman et al, 1984[32]
NCI	CTCL	T101	1 to 500	4/7	ND	Foon et al, 1983[33]
Stanford	Lymphoma	Anti-idiotype	1 to 900	5/10	6/10	Meeker et al, 1985[9]

ALL = acute lymphoblastic leukemia, AMIA = antimouse immunoglobulin antibody, CLL = chronic lymphocytic leukemia, CTCL = cutaneous T-cell leukemia/lymphoma, NO = no data

*Incidence/evaluable patients in the study
†Number of patients with objective tumor response/ evaluable patients in the study
‡Oana-Farber Cancer Institute, Boston, Mass.
§University of California, San Diego, Medical Center, San Diego, Calif.
‖National Cancer Institute, Washington, DC.
¶Stanford University Medical Center, Stanford, Calif.

the peripheral blood. Low-dose intermittent therapy was thus believed to maximize the antitumor effect while minimizing modulation. Penetration of extravascular tumor sites was documented by both Miller and associates and Foon and colleagues, usually by the occurrence of modulation rather than detectable mouse immunoglobulin.[10,20]

Although most of the toxic effects listed in Table 2 were observed, dyspnea was the most common and believed to be due to agglutination of antigen-positive cells. This was associated with a transient lung scan abnormality in one instance.[20] In more than half of the patients with cutaneous T-cell lymphoma, antimouse immunoglobulin antibodies ultimately developed, in contrast to none of the patients with chronic lymphocytic leukemia. When anti-T-cell antibodies were infused into normal primates, all recipients made AMIA.[12,34] This suggests that in the patients studied, the underlying disease and its prior therapy resulted in immunosuppression that reduced the incidence of AMIA. Clinical responses were limited to transient clearance of cells in patients with chronic lymphocytic leukemia. Half the patients with cutaneous T-cell lymphoma had objective responses including reductions in lymphadenopathy, circulating cell numbers and skin disease (Table 3). These responses were of 1.5 to 4 months' duration and often interrupted by increasing amounts of AMIA.

Ritz and co-workers reported on the treatment of four cases of relapsed common acute lymphoblastic leukemia antigen (CALLA)-positive acute lymphoblastic leukemia with J5, an IgG2a murine monoclonal antibody specific for CALLA.[19] Although dramatic reductions in circulating lymphoblasts could be observed during antibody infusions, the return of the lymphoblasts was quite rapid, and no decrease in the bone marrow infiltration was noted. Like the T65 antigen, CALLA rapidly disappeared from the surface of the malignant cells in the presence of anti-CALLA and this modulation was believed to interfere with the antitumor effect.

Antibodies against most differentiation antigens, like those discussed, presumably produce their antitumor effects by mediating cell-mediated or antibody-dependent cellular cytotoxicity (ADCC). As mouse antibodies (except perhaps IgG3) are poor at fixing human complement and only selected IgG2a and IgG3 antibodies are efficient at producing in vitro ADCC, the lack of major clinical efficacy in the studies is perhaps not surprising. Currently, trials with the Leu-1 and T101 antibodies have been discontinued. Trials with T101 antibody conjugated to drugs or toxins are contemplated.

At Stanford, 13 patients (11 previously reported) with B-lymphoid malignant disorders have been treated with monoclonal antibodies specific for the variable region or idiotype of the clonal immunoglobulin expressed on the surface of these tumors.[9] Anti-idiotype antibodies must be "tailor-made" for each patient's tumor. In these trials, IgG1, IgG2b and IgG2a antibodies have produced tumor responses in some patients. Significant amounts of paraprotein, as well as idiotype-bearing cells, may interfere with anti-idiotype therapy. Free serum idiotype antigen must be decreased either by plasmapheresis or by reducing tumor bulk. Single intravenous doses of 1 to 1,500 mg have been administered. The cumulative dose has varied from 400 to 9,250 mg of immunoglobulin. Toxic reactions were similar to those seen with anti-Leu-1 antibody and characterized by chills, fever, transient thrombocytopenia and occasional rash. The two patients who received large doses of antibody while an AMIA developed experienced the most severe toxic reactions. One of these patients had profound neutropenia during the infusions and had diffuse rashes and arthralgias. Another of these patients became hypotensive and acute tubular necrosis and a seventh cranial nerve palsy developed. In later patients the initial doses of antibody have been increased to 400 to 600 mg and no AMIA has been detected. Seven of twelve evaluable patients have had objective tumor regressions lasting from one to six months. In two of these patients tumor populations emerged that did not react with the anti-idiotype antibody.[7]

Melanoma

Melanoma has long been the subject of immunotherapeutic investigations. In malignant melanoma, there is no effective conventional therapy for metastatic disease. In rare cases, however, there are spontaneous regressions, suggesting some type of host control. Tumor nodules on the skin are accessible for biopsy and evaluation of response. A large number of surface antigens has been defined and a variety of monoclonal antibodies has been developed against each. Several centers have recently reported clinical trials with such antimelanoma antibodies (Table 4).[25,35,36] These trials have been important because they have established a number of

TABLE 4.—*Clinical Trials With Antibodies Against Solid Tumor Antigens*

Institution	Tumor Diagnosis	Monoclonal Antibody	Isotype	ADCC	Complement		Dose, mg	AMIA*	Tumor Response†	Source
					Human	Rabbit				
Sloan-Kettering‡	Mel	R_{24}	IgG3	3+	4+	...	8 to 240	+	5/12	Houghton et al, 1985[25]
NCI§	Mel	9.2.27	IgG2a	..	...	...	1 to 200	+	0/8	Oldham et al, 1984[35]
Washington‖	Mel	96.5	IgG2a	+/−	0	3+	1 to 424	...	0/5	Goodman et al, 1985[36]
	Mel	48.7	IgG1	0	0	0	1 to 212	...	0/4	Goodman et al, 1985[36]
Wistar¶	GI	17-1A	IgG2a	2+	...	...	10 to 1,000	+	3/20	Sears et al, 1982[37]
UCLA**	GI	CCOLI	IgG3	3+	4+	...	5 to 3,000	+	0/8	Lemkin et al, 1984[39]

ADCC = antibody-dependent cell-mediated cytotoxicity, AMIA = antimouse immunoglobulin antibody, GI = gastrointestinal cancer, Mel = malignant melanoma

* + = AMIA detected in all patients.
†Objective tumor response/evaluable patients.
‡Memorial Sloan-Kettering Cancer Center, New York, NY.
§National Cancer Institute, Washington, DC.
‖University of Washington/Harborview Medical Center, Seattle.
¶The Wistar Institute of Anatomy and Biology, Philadelphia
**UCLA Jonsson Comprehensive Cancer Center, Los Angeles.

facts about therapeutic monoclonal antibodies concerning the safety of administration, tissue penetration, pharmacokinetics, immunogenicity and efficacy. No intravascular antigen was detectable in any of these studies, allowing accurate determination of the dose level necessary to penetrate extravascular solid tumor sites. Single doses of more than 50 mg routinely penetrate to skin tumor nodules, initially binding to cells in the perivascular areas 16 hours after a dose. Single doses of 200 mg did not saturate the tumor cells, but ten 25-mg doses a day ultimately resulted in saturation of the tumor cell surface antigen. No modulation of these antigens was observed. The half-life of these antibodies varied between 21 and 53 hours. All of the different antibodies evoked AMIA responses. AMIA occurred transiently in one of eight patients in the National Cancer Institute study and virtually all of the patients in the other studies. These AMIA blocked in vitro binding of antibody to antigen. Most important are the differences in efficacy observed. These differences correlate with certain in vitro studies done of the therapeutic antibodies. Only R_{24}, an IgG3 antibody that mediates ADCC with human effector cells and fixes human complement in vitro, produced clinical responses. The other three antibodies of IgG1 and IgG2a subclasses were ineffective both in vitro and in vivo. These antibodies recognized different cell surface antigens. The effective antibody binds to Gb3, a ganglioside, in contrast to the glycoproteins recognized by the other antibodies that have been tested clinically.

Gastrointestinal Malignancy

In 1982, Sears and colleagues described patients treated with 17-1A, an IgG2a monoclonal antibody specific for an antigen expressed on the surface of malignant gastrointestinal tumors.[37] More than 20 patients with colonic, rectal, gastric or pancreatic tumors have received single doses of 17-1A varying from 15 to 1,000 mg.[15] Three patients with hepatic metastasis were infused via the hepatic artery, the remainder received antibody intravenously over 30 to 60 minutes. Toxic reactions were minimal, with one patient experiencing wheezing and a vasoactive reaction when infused in the presence of an AMIA response resulting from a previous administration of antibody for imaging. An interesting observation was a significant decrease in the incidence of AMIA in patients receiving large doses of antibody. In only one of nine infused with doses greater than 200 mg did AMIA develop, compared with eight of nine patients receiving a smaller dose. This might represent high zone tolerance in these patients and may signal an important approach to limiting AMIA in patients treated with other antibodies.[15] This antibody can mediate ADCC using human effector cells.[38] Because of the nature of these tumors, primarily the lack of accessible evaluable tumor and the often slow growth rate, it is difficult to evaluate the impact of antibody on the tumor in the published trials.

Another antibody that acts against a gastrointestinal tumor-related antigen is CCOL1.[39] This antibody is an IgG3 murine antibody that fixes human complement and has antibody-dependent cell-mediated cytotoxicity. Doses of up to 3 grams were infused in eight patients without severe toxic reactions. Profound declines in the C3, C4 and CH_{50} unit levels were observed during infusion of this antibody. The lack of clinical responses was perhaps related to inadequate amounts of complement, although that was not the case with R_{24}, another IgG3 antibody (antimelanoma).

Bone Marrow Transplantation: Selective Elimination of Cells In Vitro

Bone marrow transplantation has proved to be a useful treatment modality for leukemia, lymphoma and some solid tumors.[40,41] A major impediment to the use of these transplants has been the presence of contaminating tumor cells in autologous marrow or donor lymphocytes that produce graft-versus-host disease in allogeneic marrow. Monoclonal antibodies are very effective in selectively eliminating target cells from single cell suspensions in vitro. This property has been exploited to process harvested bone marrow to remove contaminating tumor cells from autologous bone marrow or T lymphocytes from allogeneic bone marrow.[42–44]

Processing of marrow must occur before cryostorage as viability will be compromised by postthaw manipulation. Antibodies plus rabbit complement or antibodies bound to a solid phase such as Sepharose (an agarose gel) or magnetic beads will remove up to three logs of unwanted cells without decreasing the viability of the remaining cells. Several sequential treatments are more effective than one. By using several antibodies specific for different antigenic determinants, more complete elimination can be achieved than with a single antibody.[42] Antibody conjugated to some toxic moiety may eliminate cells through cytotoxicity.[45]

Several institutions are conducting trials using purged bone marrow.[46-50] Hematologic recovery has not been a problem in those patients receiving treated autologous marrow. In some cases in which allogeneic marrow has been treated to minimize graft-versus-host disease, the donor marrow has failed to engraft.[50] As this problem is further studied, antibodies or procedures (or both) that selectively eliminate cells producing graft-versus-host disease and retain cells necessary for engraftment will be identified and used for purging allogeneic marrow. Unfortunately, the efficacy of autologous marrow-purging techniques is difficult to evaluate, as diseases treated in this manner are often refractory to the preparative regimen and the patient can relapse from residual disease as well as from the reinfused marrow. In addition, no data exist regarding the minimal number of contaminating malignant cells that will reseed a patient with tumor.[43]

Diagnostic Use of Monoclonal Antibodies

Imaging

Although still in the earliest phases of development, the use of specific monoclonal antibody-radionuclide conjugates is very promising. The staging information that could be obtained would influence the management of diseases such as breast cancer or melanoma through accurate noninvasive staging at diagnosis. Antibodies such as 17-1A (specific for gastrointestinal cancer), 9.2.27 and 96.5 (antimelanoma), 3F8 (antineuroblastoma) and T101 have been used to image their respective tumors after intravenous administration.[35,51-54] The problems that must be overcome to make these antibodies clinically useful are elimination of Fc binding and other nonspecific adherence, immunogenicity and ease of radionuclide conjugation. Solving these problems would eliminate background and false-positives and allow repeated administrations over time. A large variety of approaches to these problems exists and the most practical and effective must be chosen from among them.

A novel use of radionuclide-labeled antibodies is local lymphatic imaging.[55] After subcutaneous injection, monoclonal antibodies directed against a tumor entered local lymphatic vessels, passed to the draining lymph nodes and bound to localized metastatic lesions. This approach minimizes many of the problems encountered with intravenous injection, and local metastases are imaged, which is useful for staging in diseases such as breast carcinoma and melanoma. If adequate sensitivity and specificity of the data generated by this approach are achieved, surgical staging may become unnecessary.

Serum Tumor Markers

The serum concentration of tumor markers such as β-human chorionic gonadotropin and α-fetoprotein for testicular cancer and paraprotein for plasma cell myeloma reflects tumor bulk and the presence of occult disease. Bast and associates reported that blood levels of an ovarian carcinoma-associated-antigen correlated with the relative mass of ovarian tumor.[56] The small amounts of paraprotein secreted by most patients with B-cell lymphoma were undetectable using the usual clinical immunologic methods but easily quantitated with specific anti-idiotype antibody.[9] The serum concentrations of these paraproteins reflected tumor bulk.[9] As enzyme-linked immunosorbent assays are sensitive to 10 ng per ml, only small amounts of antigen need be present if the detecting antibody is specific. As a measure of occult disease, these tumor markers could be valuable in the management of certain malignant disorders.

The Future of Monoclonal Antibodies

At this time only modest advances in the care of patients with cancer have occurred as a result of monoclonal antibodies. However, in a very brief period a great deal has been learned about these proteins despite their limited use in patients. Technology has enabled us to produce the desired specificity in these antibodies but not necessarily the activity. Most of the clinical and laboratory study of antibodies in the near future will be devoted to modifications of the Fc portion of the immunoglobulin molecule designed to reduce nonspecific binding or immunogenicity or to arm the antibody with toxins, radionuclide reagents or a more effective Fc.

The most common modification of the Fc for therapeutic purposes has been to conjugate extremely potent toxins to the antibodies. One molecule of biologic toxins such as ricin, abrin or diphtheria toxin can theoretically result in the demise of a cell.[57,58] These toxins are composed of a cytotoxic A chain and a B chain that nonspecifically bind to galactose residues on the cell surface. Problems related to the nonspecific binding of the intact toxin molecule and the loss of the A-chain cytotoxic activity when the binding (B) chain is eliminated must be solved before immunotoxins are practical for in vivo administration. Ex vivo processing of bone marrow with immunoconjugates can be safely accomplished using various maneuvers not practical in vivo to protect the desired subpopulations of cells while destroying the cells recognized by the antibody.[57] Conversely, with appropriate antibodies, pluripotent stem cells desired for reinfusion into patients could be positively selected from the bone marrow. Antibodies labelled with high-specific-activity isotopes might effectively treat tumors in which the antibody localizes.[59] Isotopes that upon decay emit α or β particles would be cytotoxic to within several cells of the site to which it binds, thus limiting toxicity to adjacent normal tissues. Nonspecific accumulation of the antibody-isotope conjugate in the liver and spleen with attendant toxicity will likely result with the immunoconjugates currently available.

Other modifications of the Fc portion that have yet to be used in clinical trials are designed to reduce the immunogenicity and nonspecific binding or increase the efficacy of the antibody. Antibodies with polyethylene glycol polymers conjugated to the constant region were nonimmunogenic and exhibited minimal nonspecific binding.[60] Chimeric antibodies, produced using recombinant DNA techniques, combine the variable region of a mouse hybrid with a human Fc.[16,17] The human Fc should be nonimmunogenic and will likely mediate human effector activity much more effectively than mouse Fc. Human-human hybridomas secreting entirely human antibody could, in theory, provide the optimal monoclonal antibodies for use in humans, but several problems still exist. A practical fusion partner is not yet available. More important, no method exists for producing immunized human lymphocytes secreting antibody of a desired specificity.

Many tests will be done in large in vitro screenings to identify antibodies that will fulfill defined purposes. Because

the toxicity of antibody infusion is low and predictable and specificity predefined, future clinical trials of monoclonal antibodies must necessarily focus on efficacy. Native antibodies of interesting specificity that have no easily demonstrable in vivo antitumor activity should undergo Fc modifications, as described above, early in their development. As technology turns theory into reality, the number of useful therapeutic and diagnostic monoclonal antibodies will rapidly expand. These new cancer-specific agents can be applied in conjunction with conventional approaches for the benefit of an increasing number of patients with cancer.

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The New Biomedical Technology

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New methods for studying the genetic information of humans in health and disease are emerging from basic science laboratories. Because these approaches are yielding fundamental insights for diagnosing and treating disease, it is important that practitioners begin to understand these methods and how they are used. Methods for genetic analysis using recombinant DNA techniques consist of isolation, separation, propagation in microorganisms and molecular hybridization of DNA. The study of RNA allows determination of gene expression. These methods are being used to understand cancer, identify hereditary illness, produce pharmaceuticals and diagnose common clinical problems, such as infectious diseases.

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A great discovery is a fact whose appearance in science gives rise to shining ideas, whose light dispels many obscurities and shows us new paths.

CLAUDE BERNARD[1]

In the past ten years there have been remarkable advances in techniques for the study of the genetic information of humans and other organisms. Various terms are used to describe the general methodology of such techniques, including "recombinant DNA research," "genetic engineering" and "cloning." The time has come when these tools of the basic laboratory are immediately relevant to clinical medicine. These methods are not only being used to study disease in an entirely new light, but they are providing more precise diagnostic techniques and therapeutics. Because methods of molecular biology have only recently been introduced to clinical medicine, they may appear somewhat mysterious and even intimidating to clinicians. Therefore, the purpose of this presentation is to define these methods and describe their impact on clinical medicine. To assist in the reading of this article, a glossary of terms is given in Table 1.

Isolation and Culture of Human and Other Cells

A fundamental step in the development of molecular and cellular biology was the discovery of methods to isolate and replicate in culture cells from humans and other species.[2] This required the development of culture media, specialized glassware and incubators for growing cells. Generally, a cell culture medium consists of a solution of vitamins, minerals and other chemicals to which animal serum is added. Cells can be taken from skin or tumors and replicated in the laboratory. Nonmalignant normal cells will double only 50 or so times. This limitation has been overcome. Some cells such as blood lymphocytes can be infected with virus and "immortalized."[3] The mechanism by which viruses immortalize normal cells is unknown. However, this has the advantage of producing a cell line from any person or animal simply by drawing a tube of blood, isolating the lymphocytes and infecting them with viruses. Because these cells are immortal, they are constantly available for study and can be grown in large quantities.

How is the technique useful? One example is in the study of Huntington's disease. The ability to produce constant cell lines from families in Venezuela with a high incidence of Huntington's disease was very important in DNA studies, which resulted in developing a molecular test for the presence of the gene for Huntington's disease.[4]

Other advances in culturing of cells include techniques for freezing and banking of cells, mass culturing techniques and the development of specialized growth media that allows growth of only cells of interest, such as cancer cells.[5]

Chromosomal Analysis

In the 19th century, it became clear that the behavior of an individual cell was determined by the information contained within the nucleus of the cell. Furthermore, it was discovered that such information was carried by the cell's chromosomes.

A limiting factor during the first part of this century was that it was not clear how many chromosomes humans normally had. Not until 1956 did Tji and Leval definitively show that the normal number of chromosomes in humans was

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46—22 pairs of autosomes and 2 sex-determining chromosomes.[6] In addition, a system for grouping human chromosomes by size was developed. This was an important advance. Appreciation of the normal number of chromosomes and subclassification of chromosomes led to the discovery that certain birth defects such as the Down syndrome were due to an abnormal number of chromosomes.[7]

The next advance in chromosome analysis was techniques for staining chromosomes to identify specific regions or "bands" on the individual chromosomes. Now methods exist for elongating chromosomes so that when band-stained chromosomes are looked at under the microscope, more than 600 regions of bands can be seen on the 46 human chromosomes.[8] This detailed analysis of chromosomes increases the ability to detect chromosomal abnormalities and to relate them to disease.

These newer techniques of chromosomal analysis have been particularly important for the study of cancer. Specific abnormalities consisting of either loss of a portion of a chromosome or translocation of one chromosome region to another chromosome have been reported.[9] For instance, patients with a loss of the p13 region of human chromosome 11 have been found to have an unusually high predisposition to Wilms' tumor of the kidney.[10] Similarly, loss of a region on the long arm of human chromosome 13 has been found to lead to retinoblastoma.[11] Translocation of chromosomes is also seen in malignancy. A chromosome 3 to chromosome 8 translocation is seen in patients with familial renal cell carcinoma.[12] Of course, an abnormal chromosome 22 is familiar in patients with chronic granulocytic leukemia as the so-called Philadelphia chromosome.[13] An intensively studied chromosomal abnormality is the chromosome 8 to 14 translocation of Burkitt's lymphoma.[14] While in the past it was felt by many that these chromosomal alterations were the result of the malignant process, most investigators now feel that they are "signposts" of molecular alterations that are important in the very process of malignant transformation of cells. The translocation of chromosome 8 to chromosome 14 in malignant lymphocytes of Burkitt's lymphoma is thought to unlock the expression of an important oncogene on chromosome 8 because it is placed in proximity to the active immunoglobulin genes of chromosome 14.[15]

Finally, results of microscopic chromosomal analysis using these improved techniques have suggested at least one mechanism by which chromosome breakage, perhaps leading to deletions or translocations, might occur. Scattered throughout our chromosomes are specific sites that are particularly susceptible to breakage, termed "fragile sites."[8] Some of these fragile sites have been found at the chromosomal regions associated with malignancy.[8] It is possible that such

TABLE 1.—*Glossary of Terms in Biomedicine*

Acutely transforming retroviruses
Viruses that have incorporated oncogenes into their structure and as a consequence can malignantly transform cells that they infect

Aneuploidy
An abnormal number of chromosomes

Autoradiography
The detection of radioactively labeled molecules by their effect in creating an image on photographic film

Banding
The staining of human chromosomes with dyes, which allows microscopic delineation of specific regions of chromosomes

cDNA
Complementary DNA derived from reconstructing its genetic code from the protein of messenger RNA for which it codes

Chromosome
The discrete unit of the genome carrying many genes consisting of protein and a very long molecule of DNA visible as a morphologic entity only during the act of cell division

Cloning vectors
Plasmids, cosmids or phage into which genes are inserted for their expansion

Deletion mutant
A cell containing only a fragment of a particular chromosome

DNA [deoxyribonucleic acid]
The chemical component of the cell that encodes the genetic message of the cell

DNA probe
An isolated, expanded DNA sequence that can be used to examine other sequences to determine whether complementary sequences are present, absent or altered

Eukaryotic cells
Cells containing a limiting membrane around their nuclear membrane, as compared with prokaryotes, which do not have such a membrane

Ideotype
The idealized human chromosome karyotype

In situ hybridization
A recombinant DNA technique whereby DNA probes are hybridized directly to intact chromosomes

Kilobase
1,000 bases. A term used to describe the length of DNA molecules; for example, 7.1 kilobases (kb) equals 7,100 bases

Nick translation
The process of labeling, usually with radioisotopes, a DNA probe so that it can be detected

Oncogenes
Gene sequences present within cellular DNA that are able to code for molecular products that cause the malignant transformation of cells; literally, cancer-causing genes

p region
The short arm of a chromosome

q region
The long arm of a chromosome

Recombinant DNA libraries
A collection of cloning vectors containing various portions of genetic material of interest

Reiterated sequence DNA
DNA sequences that are highly prevalent throughout genetic structure but which do not code for specific molecules. Their function is unknown

Restriction
The process of cutting DNA with restriction endonucleases

Restriction site polymorphism
A genetic marker based on the fact that DNA from different persons may be cut into different sizes by a particular restriction endonuclease

Restriction map
The result of separation of DNA fragments in gels after they have been cut with restriction endonucleases

Reverse transcriptase
The enzyme that catalyzes the synthesis of DNA on a template of RNA

RNA [ribonucleic acid]
A macromolecule formed from DNA templates. A particular form of RNA termed messenger RNA (mRNA) carries the active DNA message for protein production.

Somatic cell hybrid
The result of fusion of two different cells (usually from different species) to form a new cell line containing all or part of the genetic information from parent cells

Southern blot
The result of transferring DNA from a gel to filter paper

Unique sequence DNA
DNA sequence coding for a particular protein

sites may provide targets for mutagenic agents, such as radiation. Thus, breakage of the chromosome may be an important step in the development of some malignant processes.

Somatic Cell Hybrids

An important technique for the study of particular chromosomes was the production of somatic cell hybrids.[16] This allows separation of a human chromosome of interest from other human chromosomes. Figure 1 illustrates this process. To form hybrid cells, human cells are fused with rodent cells, usually Chinese hamster or mouse. The fused hybrid cells are then grown under conditions of cell culture that select against parent human and rodent cells and allow growth of only hybrids that contain the human chromosome of interest. The result is a cell that contains the particular chromosome on a background of rodent chromosomes. An important application of this technique has been in gene mapping—that is, the assignment of specific genes to individual chromosomes.[17] Furthermore, it is a mechanism by which chromosomes associated with clinical disorders can be isolated for study. An example is chromosome 21. Production of somatic cell hybrids containing this chromosome has allowed studies of chromosome 21 aimed at identifying the biochemical abnormalities that lead to Down's syndrome.[18]

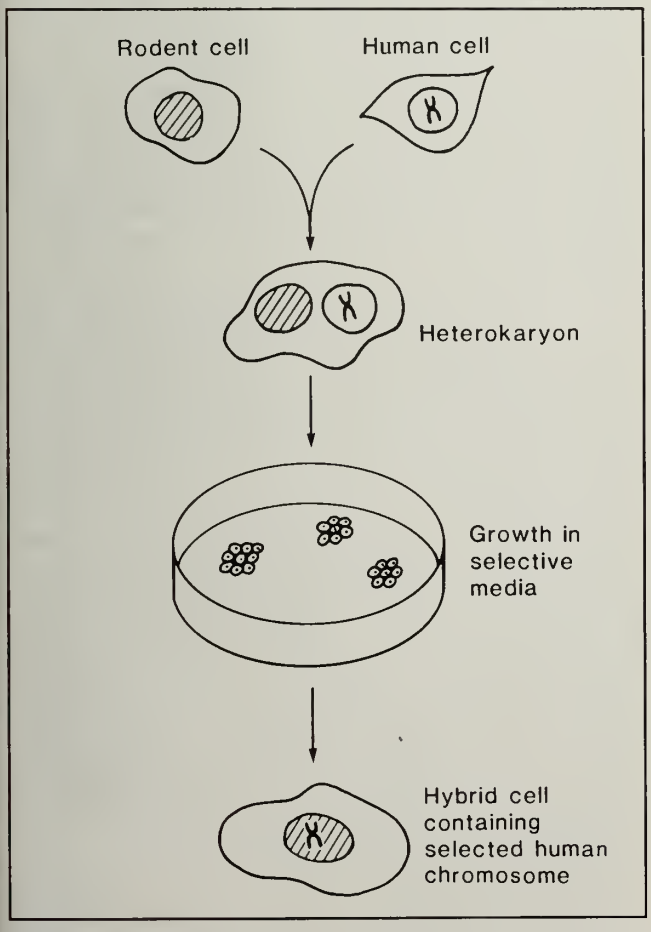

Figure 1.—Production of a somatic cell hybrid. A human cell is fused with a rodent cell using a fusing agent such as a virus or polyethylene glycol. Resulting hybrid cells are grown under conditions of cell culture such that eventually a cell clone is produced that isolates the human chromosome of interest in the rodent cell. (From Scoggin and Fisher.[19])

DNA Isolation

While somatic cell hybrids provide a method whereby individual chromosomes can be isolated, modern techniques of molecular biology allow us to go even further—we can isolate particular genes. An important methodology is isolation and purification of DNA from cells of interest. DNA can also be isolated from the cells in the peripheral blood of patients. Skin biopsies, tumors and cell cultures can also be used. Similarly, DNA can be obtained from other microorganisms such as bacteria, viruses, parasites and mycobacteria. To isolate DNA, cell walls are disrupted enzymatically, protein digested and extracted and the DNA precipitated. This process is well standardized and requires no complexity of equipment beyond a centrifuge. DNA thus purified can be stored where it is readily available for a number of experimental tests.

DNA Separation

To accomplish many of the studies involving DNA, DNA must first be separated into usable pieces. This is done with the use of specialized enzymes called "restriction enzymes" and DNA agarose gel electrophoresis.

Restriction Enzymes

Bacteria possess enzymes that protect them from invasion by foreign DNA. These are restriction enzymes.[20] Many restriction enzymes have been isolated from various bacteria and take their names from the bacteria from which they are isolated. Thus, the enzyme "Eco R1" was isolated from *Escherichia coli (E coli)*. The power of each restriction enzyme is that they recognize and cut DNA at only a specific site in the DNA nucleotide code. For instance, the enzyme Eco R1 will only cut DNA when it sees the nucleotide sequence GAATTC. Restriction enzymes vary in the size of DNA pieces they cut. The enzyme Mbo 1 cuts DNA many more times than Eco R1. To use a very simplistic analogy, using restriction enzymes is somewhat like searching a haystack for a needle. If one wishes to search a haystack, it is helpful to divide the haystack into smaller haystacks. Restriction enzymes accomplish this with DNA. Different restriction enzymes divide DNA into different-sized pieces (or "haystacks"). These enzymes are available commercially and their use is now fundamental in DNA study.

Agarose Gel Electrophoresis

Once the DNA to be studied is cut by restriction enzymes, it must be separated by size, which is accomplished by using agar as a molecular sieve. A gel of agar is poured, the DNA sample to be separated is placed in wells at the top of the gel and a current applied across the gel. This current causes the DNA to move through the gel. The distance a piece of DNA will travel over time is determined by its size. Smaller pieces of DNA will move faster than larger. The result is that the pieces of DNA are separated out throughout the gel, with larger pieces at the top and smaller at the bottom. Fragments of DNA of known size are run as standards parallel with the DNA so that it is known where in the gel DNA samples of a particular size are located. DNA size is expressed in kilobases or kb. Usually DNA is separated from sizes of 50 kb to less than 1 kb. More recently, a technique called "orthogonal field alternation gel electrophoresis" (OFAGE) has been de-

veloped that allows separation of very large pieces of DNA (up to 1,000 kb).[21] This is an important advance because it allows investigation of much larger portions of the genome at a time. This technique has recently been used to determine the actual number of chromosomes contained by the parasite *Plasmodium falciparum*—a necessary step in understanding this important human parasite.[22]

Southern Blotting

Another fundamental technique of DNA research is the Southern blot.[23] Taking its name from E.M. Southern of Edinburgh who developed the technique, it is a method by which DNA is removed from the agarose gel in which it has been separated by size. This is necessary because working with DNA in the gel is very difficult. To accomplish Southern blotting, a piece of nitrocellulose filter paper (or some other matrix such as nylon) is placed over the gel containing the DNA and the DNA transferred onto the paper by drawing a buffer through the gel and filter paper by capillary action. Thus, the DNA is literally blotted onto the filter paper. This process takes 4 to 18 hours. Alternatively, an electric current can be applied across the gel-filter to speed the process. This is termed "electroblotting." DNA transferred to the nitrocellulose or other filter is strongly bound. It represents a replica of the agarose gel, but is much easier to work with. If DNA need not be separated by size, it can be directly applied to the nitrocellulose. This is termed "dot blotting."

To summarize to this point, DNA can be isolated from any nucleated cell; this DNA can be cut into predictable, usable pieces by specialized restriction enzymes. The DNA can then be separated by size by the use of agarose gel electrophoresis. Finally, to facilitate study of the DNA, it is then transferred onto nitrocellulose or other matrix by a process termed Southern blotting.

RNA Isolation and Analysis

Analysis of a messenger RNA (mRNA) provides a method by which genes can be isolated and gene expression studied. Just as the DNA can be isolated from cells, so too can RNA. Additional care must be taken to protect RNA from degradation by ribonuclease enzymes. This is done by adding chemicals or enzymes that inactivate ribonuclease. Messenger RNA must be separated from other types of RNA, which is done by using affinity columns that bind mRNA. Most commonly this is accomplished by a process called "oligo dt chromatography."[24] Isolation of mRNA is important because it can be used to analyze gene expression. Because mRNA is the result of gene expression, it can literally tell investigators which genes are being expressed and in what amounts.

Cloning of Genes

The ability to clone genes basically relies on isolating DNA, cutting DNA with restriction enzymes, cloning vectors to carry DNA, inserting foreign DNA into cloning vectors and using specialized microorganisms for expansion of the cloning vectors containing the "cloned" gene of interest.

Cloning Vectors

Cloning vectors are literally gene carriers. They are plasmids or viruses into which foreign DNA can be inserted. Gene carriers have even been invented, such as cosmids, that allow larger pieces of DNA to be cloned than could be accomplished with virus or plasmids.[26] The availability of restriction enzymes that leave "sticky ends" when they cut DNA has greatly added to the effectiveness of this process of gene cloning.

To clone genes, the cloning vector is cut open with a restriction enzyme that leaves sticky ends. The piece of DNA to be inserted is either cut with the same enzyme to yield similar sticky ends or such sticky ends are attached onto the end of the DNA to be cloned. The DNA to be inserted and the gene carrier are then reacted together and the foreign DNA ligated or "recombined" with the gene carrier. The recombinant vector with the inserted gene is then inserted into a host bacterium that serves as a minifactory in which to grow the gene carrier and its inserted genetic sequence in quantity. By use of selectable markers, such as antibiotic resistance, bacteria containing the gene carrier of interest can be readily identified and isolated. The bacteria used are specialized strains that cannot grow outside of a laboratory environment—a precaution to prevent unnecessary environmental introduction of cloned genes.

DNA for cloning can come from many sources. For instance, it is possible to isolate the messenger RNA coding for a gene of interest and then use an enzyme called "reverse transcriptase" to read the genetic code backwards to produce a complementary DNA (cDNA) sequence of the gene that can then be cloned into a vector such as a plasmid.

All the mRNA from an entire organ, such as liver, can be made into cDNA and cloned into vectors to produce a cDNA "library" of that organ. Such a library would presumably contain the cDNA sequences of all genes expressed by that organ. Thus, the term "library" points out that all the expressed genes have been placed into a collective within cloning vehicles.

Intact DNA itself can also be cloned to form a library. For instance, it is possible to extract the DNA from an entire organ or cell line, cut it with a restriction endonuclease and insert all that DNA into a gene carrier. Because this library would contain all the genetic sequences in the cell, not just those that are expressed as mRNA, it is much more complete than a cDNA library. Such libraries are known as "genomic libraries."[27]

Libraries can even be made of particular chromosomes. For instance, as mentioned earlier, somatic cell hybrids can be used to isolate individual human chromosomes, such as human chromosome 21.[18] A library can be made directly of the DNA from the hybrid. This library will contain both human and hamster sequences—yet this library can be "screened" and the human chromosome members of the library identified and isolated. Alternatively, a specialized machine using lasers can first sort the human chromosome from the hamster chromosomes.[28] The isolated human chromosome DNA can then be used to construct the library.

The ability to clone DNA has been one of the most important advances in molecular biology. It has not only allowed isolation and study of particular genes but has led to industrial methods for producing large amounts of desirable proteins such as insulin. It has also provided a method by which desirable traits can potentially be introduced into food sources. It has also allowed the isolation of genes that appear to be very important in malignant disorders—oncogenes.[29]

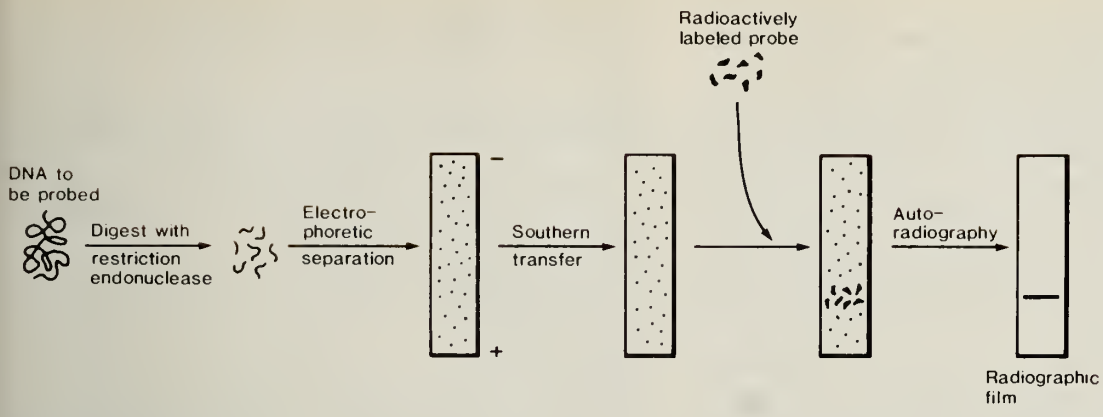

Figure 2.—Southern analysis: DNA to be studied is first digested with a restriction enzyme. DNA is separated by size through agar and then blotted onto nitrocellulose. The Southern blot is then reacted with a radioactive probe. If DNA hybridization has occurred, it will appear as a band of radioactivity when the blot is exposed to radiographic film. (From Scoggin and Fisher.[19])

Gene Analysis

By the use of genetic probes, we are able to peer into the very molecular structure of genes and determine how they are affected by disease. Three important techniques for such analysis are "Southern analysis," "restriction fragment-length polymorphism" and "DNA sequencing."

Southern Analysis

Southern analysis is summarized in Figure 2. As mentioned previously, restriction enzymes cut DNA into useful pieces, agarose gel electrophoresis separates cut DNA by size and Southern blotting removes the DNA from the separation gel onto a membrane surface called a Southern blot. This blot can then be probed with a gene or DNA sequence of interest to find out if the DNA on the blot contains the gene or DNA corresponding to the probe. This is called DNA hybridization and relies on the fact that pairing of nucleotide bases within the double-stranded DNA molecule occurs according to the rules of the genetic code, such that adenine must always pair with thymine and cytosine must only pair with guanine. If the genetic code of the probe does not find its counterpart in the DNA on the Southern blot, hybridization will not occur.

To accomplish such hybridization, the DNA on the Southern blot is rendered single-stranded by treatment with strong alkali. The DNA probe is labeled with radioactivity, or some other tracer, and it is made single-stranded by boiling. Temperature causes DNA double strands to disassociate or "melt" into single strands. The labeled probe and Southern blot are then placed in a plastic bag and allowed to react together, usually overnight. If the probe finds its counterpart on the Southern blot, hybridization will occur. The blot is then washed. Wherever probe has found its complementary DNA sequence, it will not be washed off. If radioactivity has been used as a probe's label, when the Southern blot is exposed to radiographic film, exposure will occur and a "band" will be seen on the film. Because disease will sometimes alter the size of a gene or where a restriction enzyme cuts the gene, not only is it important to know whether or not a gene is present in a DNA sample, but also its size. Both these pieces of information can be determined by Southern analysis.

Restriction Fragment-Length Polymorphism

Restriction fragment-length polymorphism is a somewhat formidable term for what is really a rather simple but important concept. It allows construction of genetic maps of DNA and correlation of such maps with particular traits—a recent example being Huntington's disease.[4]

A polymorphism is the coexistence of more than one variant of a particular trait. A restriction fragment-length polymorphism refers to the fact that the DNA from any particular region in different persons may be cut into different-sized pieces by the same restriction enzymes. This will result in bands of DNA on a Southern blot appearing at different levels. This type of blot is a "restriction map." Polymorphisms in the genome can be detected by comparing the restriction maps of different persons. A difference in restriction maps between two persons can be used like any other genetic marker. The only difference is that the DNA itself is examined at the molecular level and not somatic phenotypic markers such as blood group or eye color. It is an extremely powerful technique. In the future, a genetic map of the human genome will probably be constructed that will allow detection of carrier and affected persons with such important disorders as cystic fibrosis. Restriction fragment-length polymorphism also allows identification of the particular chromosomal region that carries the genes responsible for the disorder—an important step in understanding the molecular basis of any disease.

DNA Sequencing

Not only can DNA be isolated and characterized by size and restriction pattern, the actual sequences of the base pairs that make up DNA can also be ascertained. This is literally "decoding" DNA. Protocols are now available by which DNA can be either chemically cleaved or synthesized in such a way that at each step the involved nucleotide base sequentially affected is known.[30] Step by step the sequence of the DNA of interest is determined. This is now such an accurate procedure that DNA molecules of 300 base pairs or even larger are more easily analyzed than the proteins sequenced for which they code. With the use of computers, DNA sequences of various genes are being made widely available for scientific comparison. This sequence information has also allowed the development of technology to synthetically produce genes or parts of genes.

Summary

While in the past it has been rightly said that basic science and clinical medicine are on a collision course, it can now be legitimately stated that the collision has occurred. Molecular biology has given us a whole new microscope with which to

study human disease and every other type of biologic phenomenon. Southern blots showing the basic investigation of such clinical disorders as cancer and infection are now regularly seen in medical journals. Useful genes such as those for insulin and growth hormones have been cloned and their products made available as pharmaceutic agents.[31] Other genes are also being isolated for production—such as α_1-antitrypsin for persons with congenital deficiencies of the enzymes and premature emphysema.[32] Experiments are even being conducted to change the site on the α_1-antitrypsin molecule that is subject to biologic degradation. This involves a process called "site-directed mutagenesis," which induces a change in the genetic code for the enzyme.[32] If it is successful, it would be somewhat like instant evolution to produce a more effective enzyme than what would normally occur. DNA probes for infectious diseases are also being introduced into the clinical laboratory.[33] The result will be faster, cheaper and more accurate tests.

DNA hybridization has provided improved tests for such hereditary disorders as sickle cell anemia and thalassemia.[34-36] Diagnostic tests for other important hereditary disorders such as Huntington's disease and cystic fibrosis are being developed or sought. The ultimate payoff, however, is not going to be just improved diagnostic and pharmaceutical production. While an important advance, producing human insulin does not cure diabetes. The reward of this new technology will be in the understanding and methodologies that are to come that will allow entirely new strategies for directly correcting the metabolic malfunction of disease.[37] It is reasonable to speculate that in the future, physicians will be able to intelligently manipulate the biochemistry of the body in a way analogous to how a surgeon now manipulates organ function.

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The Molecular Biology of Chromosome Alterations in Myelogenous Leukemia

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In the past few years, new developments have rapidly emerged that promise to unravel the pathogenesis of malignant transformation. By understanding the molecular events in neoplastic transformation, such as in myelogenous leukemia, we should be able to devise specific and effective therapies and to intervene in the development of these diseases. Furthermore, the study of cancer genes is likely to have far-reaching effects with regard to our understanding of normal development and other nonneoplastic conditions.

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A large body of literature has rapidly emerged concerning the isolation and characterization of transforming genes, or oncogenes, that appear to be at least in part responsible for the development of various malignant diseases. These advances have been made possible by basic research in a wide range of disciplines, many of which had no initial obvious connection with cancer per se. DNA transfection experiments, which consist of introducing tumor DNA into recipient cells and isolating transformed foci, have shown the frequent occurrence of an altered *ras* oncogene product in a wide variety of tumors, including acute leukemia. Thus, the *ras* oncogene appears to be commonly involved in either tumor initiation or tumor progression. The observation that chromosome rearrangements were nonrandomly associated with specific malignant diseases suggested that genes located at or near the sites of these rearrangements would be involved in the transformation process. Before discussing some of the developments in the myeloid leukemias, it is worth reviewing one of the most studied malignant diseases to date, namely Burkitt's lymphoma.

Burkitt's lymphoma is characteristically associated with a reciprocal exchange of chromosome material between chromosomes 8 and 14. Less frequently, this translocation occurs between chromosomes 2 and 8, or chromosomes 8 and 22. One of these translocations is present in virtually every case of Burkitt's lymphoma. Through the technique of somatic cell genetics, it was possible to separately isolate these chromosomes in rodent-human cell hybrids.[1] What was found was that the c-*myc* oncogene normally located on chromosome 8 at the site of rearrangement had been translocated next to immunoglobulin genes on chromosome 14. In the case of the variant 8;22 and 2;8 translocations, the c-*myc* oncogene remained on chromosome 8 but was juxtaposed to immunoglobulin genes from either chromosome 2 or 22, which had moved to the other side of c-*myc*.[2,3] Using recombinant DNA techniques, several investigators were able to clone and identify the actual site of recombination from different Burkitt's lymphomas and to determine the effect of the translocation on the expression (messenger RNA) of c-*myc*. Although significant variations in the actual site of recombination were observed, a unifying concept emerged that deregulation of c-*myc* expression resulted from the translocation.[4,5] The product of the c-*myc* gene is a nuclear binding protein that is intimately associated with cell proliferation.[6] It is felt that increased cell division is a result of deregulated c-*myc* expression. In Burkitt's lymphoma, the altered c-*myc* expression, due to the influence of immunoglobulin genes, is tissue specific and, depending on the translocation, may be differentiation specific as well,[4,7] Thus, the translocated c-*myc* gene is only abnormally expressed in B lymphocytes. This is an important observation and has broad implications for the isolation of transforming genes using a transfection assay. The existence of cloned immunoglobulin gene probes allowed the isolation of a new flanking DNA sequence that in this case turned out to be c-*myc*.

Recently, two additional translocations have been isolated and cloned in a similar manner. The 14;18 translocation is present in most cases of nodular lymphomas and the 11;14 translocation is seen in diffuse small and large cell lymphomas.[8,9] In both cases, putative oncogenes from chromosomes

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11 and 18 have been isolated.[10,11] Like c-*myc*, these genes have been translocated to the immunoglobulin heavy-chain region on chromosome 14 that facilitated their cloning. The normal function of these genes and functional changes resulting from the translocation are under intense investigation.

With this background in mind, we shall now examine some of the molecular alterations in the myeloid leukemias.

Chronic Myelogenous Leukemia and the Philadelphia (Ph¹) Translocation

Chronic myelogenous leukemia is associated with a specific translocation, t(9;22)(q34;q11), in more than 90% of patients.[12] In the remaining cases, either a three-way variant translocation occurs, or there is no translocation—that is, Ph¹-negative chronic myelogenous leukemia. The Ph¹ chromosome refers to a deletion in the long arm (q) of chromosome 22 resulting from the translocation of 22q material to the long arm of chromosome 9. This was initially shown by Rowley and was the first specific chromosome abnormality identified in malignant disease.[13] In patients with chronic myelogenous leukemia, a chronic phase usually persists for about three years, followed by an accelerated phase ending in blast crisis. This accelerated and blast crisis phase is associated with additional nonrandom chromosome alterations. The most frequent changes are a second Ph¹ chromosome; an isochromosome 17, consisting of both long arms of 17 joined at the centromere, and an extra chromosome 8. These secondary changes appear to represent a mechanism of tumor progression.

Using somatic cell hybrids and in situ hybridization experiments, investigators were able to determine that the c-*abl* oncogene, normally located on the long arm of chromosome 9, had been translocated to the 22q− chromosome.[14] In fact, in variant three-way translocations, this is the constant feature, namely, the movement of c-*abl* to the 22q−.[15] In Ph¹-negative chronic myelogenous leukemia, there is no translocation of c-*abl*.[14] This is consistent with the concept that Ph¹-negative chronic myelogenous leukemia is a different disease associated with a poorer prognosis.

Investigators were able to clone the actual site of rearrangement, which led to an important observation. The normal c-*abl* oncogene is large (32 kilobases [kb]) and the breakpoint occurs in the 5′ portion of the gene, although the site of rearrangement varies considerably among different cases of chronic myelogenous leukemia. The chromosome 22 region where the break occurs is quite limited, however.[16] Most rearrangements can be shown to occur within a 5.8-kb segment, referred to as the breakpoint cluster region, or bcr. This finding suggests that both chromosome regions are critical to the biology of the translocation. Unlike the Burkitt's lymphoma translocation, the chromosome 22 bcr region has no homology to immunoglobulin genes. Neither is there homology to the c-*sis* oncogene that has been mapped to chromosome 22, although more distal to the breakpoint. In fact, there is no evidence to date that c-*sis* has any role in the development of chronic myelogenous leukemia.

Despite the variability in the c-*abl* breakpoint, the translocation results in a single new species of c-*abl* RNA.[17] Nonchronic myelogenous leukemia hematopoietic cells contain two c-*abl* RNA species of 6 and 7 kb. In chronic myelogenous leukemia, a new 8-kb message can be detected, either as the only RNA species or in combination with the 6- and 7-kb transcripts. This larger message results from a chimeric or fused gene consisting of the bcr region joined to the altered c-*abl*. The obvious question is how this alteration might be pathogenic. The c-*abl* oncogene also exists, in an altered form, in an acutely transforming RNA tumor virus. This virus produces predominantly an acute pre-B-cell leukemia. The transforming ability of this v-*abl* gene is due to a tyrosine kinase activity in the v-*abl* protein. Using similar assays, however, the normal c-*abl* gene does not possess tyrosine kinase activity. The change in function between the normal cellular gene and the viral oncogene appears to result from an alteration in the 5′ portion of the gene. In chronic myelogenous leukemia, the abnormal 8-kb messenger RNA gives rise to a larger than normal 210,000-dalton protein referred to as P210 c-*abl*. Like the viral *abl* protein, P210 c-*abl* also has tyrosine kinase activity. It is believed that an alteration in the 5′ region of the gene, resulting from the translocation, unmasks or deregulates this kinase activity, leading in part to the development of chronic myelogenous leukemia.[18] This abnormal protein may provide a specific target for future therapy. Compared with the Burkitt's lymphoma translocation that results in abnormal expression of a normal protein, the chronic myelogenous leukemia translocation results in a qualitative alteration in the protein. Again, despite heterogeneity in the actual site of recombination, a common alteration appears to result. This is important and suggests that specific interventions may be effective in most patients who have chronic myelogenous leukemia.

The development of malignancy is felt to be a multistep process. Chronic myelogenous leukemia appears to be a case in point where there is some evidence that alterations may occur before the translocation arises. In a multistep pathway, it may not be necessary to uncover every step before discovering a solution. Of course, the more information that is known regarding these alterations, the higher is the likelihood of developing such an intervention.

The M2 Subtype of Acute Myeloblastic Leukemia and the 8;21 Translocation

Before the advent of chromosomal banding, a group of patients with acute myeloblastic leukemia was described possessing a chromosome abnormality referred to as the complex profile and similar disease characteristics. With quinacrine banding, Rowley was able to show that this abnormality represented a reciprocal translocation between chromosomes 8 and 21 at the bands 8q22.1 and 21q22.3.[15] Of interest, this translocation is specific for the M2 subtype of acute myeloblastic leukemia—that is, acute myeloblastic leukemia with maturation. Of patients with de novo acute myeloblastic leukemia and the M2 subtype, approximately 18% have the t(8;21). If one considers only those patients with the M2 subtype and detectable chromosome abnormalities, then about a third have the t(8;21). Of particular interest is that the chromosome 21 region involved in this translocation is the region required to be trisomic to produce the Down syndrome phenotype. Moreover, patients with Down's syndrome have a greatly increased risk of leukemia. Another observation is that neonates with Down's syndrome may have at birth what appears to be acute leukemia, except that spontaneous resolution of this syndrome is the rule. Some of these persons have

shown a mosaic pattern for trisomy 21. In these cases, the "blast cells" contained the trisomy 21 clone, suggesting that this population of cells possessed a growth advantage. Furthermore, in complex three-way 8;21 translocations, the constant feature is the movement of chromosome 21 material to the 8q− chromosome.[15]

These observations suggest that a gene(s) on chromosome 21 may be involved in the growth and regulation of hematopoietic cells. We have isolated both translocation chromosomes in separate somatic cell hybrids. We have found that there is an oncogene on chromosome 21, that it is in the appropriate region and that it is translocated to the 8q− chromosome in this disease. (The details of this will be published elsewhere.)

An additional oncogene, c-*mos*, has been localized to the region of chromosome 8 where the rearrangement occurs.[19] For this gene, we have shown that it remains on chromosome 8, and we have not detected any rearrangements in several patients examined so far.[20] Because a cytogenetic band contains about 5 million base pairs of DNA, it is easy to see how translocations may involve a particular band and yet be located at a great distance from a similarly localized DNA sequence.

Until recently, c-*mos* RNA had never been detected in any human tissue, tumor or cell line. Recently, investigators have been able to detect c-*mos* transcripts in a variety of tissues.[21] The highest level seems to be present in gonadal tissue, and different-sized transcripts are present in different tissues.

The 8;21 translocation of acute myeloblastic leukemia is associated with a high incidence of the loss of a sex chromosome. This loss has been shown to be a secondary change developing after the 8;21 translocation.[22] The X and Y chromosomes are known to contain some gene duplications. Although speculation, the function of c-*mos* may have to do with some aspect of sexual function or development. The loss of a sex chromosome might conceivably influence c-*mos* expression. Alternatively, altered c-*mos* expression may result from the 8;21 translocation and could be further influenced by such a loss. Since c-*mos* expression has now been reported, it should be possible to answer such questions. Present information suggests that c-*mos* has protein kinase activity. Unlike c-*abl* and c-*src* kinase activities that phosphorylate predominantly tyrosine residues, c-*mos* phosphorylates serine and threonine residues. Recent evidence has shown that c-*mos* has homology to the epidermal growth factor (EGF) precursor molecule and also to a cell-cycle-specific gene in yeast, CDC-28.[23,24] It is postulated that the pro-EGF molecule might function in cell-cell interactions.

It should be noted that the chromosome 21 oncogene may be involved in producing the Down syndrome phenotype. Again, the study of cancer genes without doubt will greatly influence our understanding of many other abnormalities and vice versa.

Acute Promyelocytic Leukemia and the 15;17 Translocation

Acute promyelocytic leukemia has been of particular clinical importance because of its high association with disseminated intravascular coagulation. Recognition of this subtype is important because low-dose heparin therapy may prevent fatal hemorrhage. A microgranular variant has been described wherein the granules are too small (<250 nm) to be seen by light microscopy. Acute promyelocytic leukemia is characteristically associated with a reciprocal translocation between chromosomes 15 and 17, t(15;17)(q22;q21.1). There is good evidence that all patients with acute promyelocytic leukemia have the t(15;17). The *erb*-A oncogene has been localized on chromosome 17 proximal to the breakpoint, but there is yet no evidence linking *erb*-A to acute promyelocytic leukemia.[25] Chromosome 15 also contains the c-*fes* oncogene, but this is located far distal to the breakpoint. Recently, the cellular tumor antigen p53 has been localized to bands 17q21-q22, the region where the breakpoint occurs, and is translocated to the 15q+ chromosome. A role for p53 in acute promyelocytic leukemia is suggested by this information, and, moreover, this appears to be the conserved abnormality in variant translocation.[26]

Acute Myelomonocytic Leukemia (M4) With Associated Bone Marrow Eosinophils and Abnormalities of Chromosome 16

LeBeau and others have described a rearrangement of chromosome 16, frequently a pericentric inversion, inv(16)(p13q22), that is highly correlated with a variant type of myelomonocytic leukemia.[27] In this variant, there are cells with eosinophilic characteristics but with abnormal morphology and cytochemistry. The nucleus may be folded, resembling a monocyte, and the cytoplasmic granules may be predominantly eosinophilic or basophilic. The positive reaction of these granules with periodic acid-Schiff and chloracetate esterase is atypical. It may be that these cells represent stages of differentiation in the leukemia cell. Of clinical interest is that patients with this pattern appear to have a prolonged remission.

The metallothioneins are proteins known to bind and protect against heavy metals. These proteins may also function as regulators of growth and differentiation by binding enzyme requiring metal ions.[28] The chromosome 16 inversion has been shown to split the cluster of metallothionein genes present on chromosome 16. Some of these patients have a rearrangement in the gene structure demonstrable by Southern blots. Investigators are attempting to isolate one of the rearranged genes and to determine if an oncogene has been activated.

Abnormalities of 11q in Monocytic Leukemia

Translocations or deletions in the long arm of chromosome 11 appear to be associated predominantly with monocytic leukemia.[12] The breakpoint is usually in band 11q23-24, but may also be in 11q13-14. The most common translocation involves the short arm of chromosome 9 at p22 and the long arm of chromosome 11 at q23—that is, t(9;11)(p22;q23). Of interest, the *ets* oncogene is normally located on chromosome 11 at band q23. In situ hybridization studies have recently shown that this oncogene is translocated to chromosome 9, although a rearrangement of the gene was not detected in this particular case.[29] The oncogene *ets* was isolated from the RNA tumor virus E26. This virus carries two oncogenes, *myb* and *ets*. Another retrovirus, avian myeloblastosis virus, produces a pure myeloid leukemia and contains only the *myb* oncogene. The E26 virus produces predominantly an erythroid leukemia, although transformed myeloid cells can be

shown. The *ets* gene is apparently responsible for the enhanced spectrum of activity.[30]

A high correlation has recently been described between acute lymphoblastic leukemia with bulky disease and abnormalities of the short arm of chromosome 9.[31] This region is the same one involved in the 9;11 translocation described above. Thus, isolation of the 9;11 breakpoint may have implications for acute lymphoblastic leukemia as well.

Secondary Leukemias and Myelodysplastic Syndromes

The secondary leukemias and myelodysplastic syndromes constitute a heterogenous group of diseases and will not be covered in detail. The development of secondary leukemia or a myelodysplastic syndrome after treatment is usually fatal and is an all-too-frequent complication. The large majority of such cases have a deletion of part or all of chromosome 5, chromosome 7 or both. These chromosome abnormalities also occur in de novo acute myeloblastic leukemia but usually in an older age patient. This suggests that a similar cause may be involved in both groups.

A myelodysplastic syndrome referred to as the "5q-syndrome" consists of refractory anemia, myeloid hyperplasia, hyperlobulated megakaryocytes and peripheral thrombocytosis. Many of these patients have progression to acute leukemia. The oncogene c-*fms* has localized to chromosome 5 near the deletion. A 5q− chromosome has been isolated from one patient and loss of the c-*fms* oncogene was shown. The c-*fms* oncogene is related to and may be identical with the receptor for the hematopoietic growth factor CSF-1.[32] This factor is involved in the differentiation and proliferation of primitive hematopoietic cells. It is possible that an abnormality of the CSF-1 receptor could lead to myelodysplasia. This is an exciting observation that is likely to shed light on this group of diseases.

In summary, significant and rapid progress in understanding the pathogenesis of malignant disease has been made, but we are witnessing only the beginnings of the results. It is to be stressed again that cancer research and other basic research go hand in hand. The goal of this research is to understand the basic mechanisms that will lead to specific therapies and interventions to interrupt the disease process. Such research will have broad implications for many diseases and developmental abnormalities as well.

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Combined Heart and Lung Transplantation

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Combined heart-lung transplantation has now been carried out in 27 patients at Stanford University Medical Center. All recipients had suffered from pulmonary hypertension, either primary or the result of Eisenmenger's syndrome. The one-year survival has been approximately 70%. All survivors returned to normal activity, though later respiratory difficulty has been encountered in some of these patients and has required retransplantation in one. These late occurrences are likely the result of inadequate control of rejection.

Heart and lung transplantation has been shown to be an effective therapy for otherwise progressively fatal pulmonary conditions, and, in the case of Eisenmenger's syndrome, has presented a therapeutic avenue for the first time. The late complications encountered in some of these patients can probably be averted with increased experience.

(Jamieson SW: Combined heart and lung transplantation, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:829-833)

End-stage parenchymal or vascular pulmonary diseases are progressively fatal, and treatment is only palliative in the later stages. Transplantation, for the first time, has presented a therapeutic option that is potentially curative.

Many efforts were made in the past to achieve single-lung transplantation, without success. Of approximately 38 patients, 2 survived more than one month.[1] One lived for six months and the other ten months but, apart from a two-week period in the latter patient, both remained in hospital throughout their postoperative course. Before 1980 there were also three attempts at combined heart and lung transplantation.[2-4] All three combined heart-lung recipients died within a few days.

Although heart and lung transplantation had been done in the laboratory at Stanford in 1961,[5] it was 20 years before the operation was attempted clinically at this center. The intervening period, however, was invaluable to the final achievement of success in this field. In the ten years that preceded the start of clinical heart transplantation at Stanford (in 1968), laboratory investigators found satisfactory techniques for preserving the heart during transplantation and established methods for the diagnosis and treatment of graft rejection. After the inception of the clinical program, continued research led to several major improvements in management, including the introduction of rabbit antithymocyte globulin,[6] the endomyocardial biopsy technique for diagnosing rejection[7] and methods for monitoring the immunologic state of patients.[8] By 1980, some 250 orthotopic clinical heart transplants had been done at Stanford.

When cyclosporine became available,[9] studies with this drug in our laboratory included cardiac allografts in rats[10] and the first use of cyclosporine in primates.[11] As a result of these studies, an immunosuppressive protocol incorporating cyclosporine was begun in cardiac transplant patients in December 1980.[12] Because, in addition to providing superior immunosuppression to azathioprine and steroids, cyclosporine also allows nearly complete tissue healing so that airway dehiscence—historically a major obstacle to long-term pulmonary allotransplant survival—became less likely, it seemed a natural step to reattempt heart-lung transplantation in the laboratory.

The first long-term survival after cardiopulmonary allografting in primates was then achieved.[13] In all, 27 monkeys underwent cardiopulmonary transplantation with the use of cyclosporine immunosuppression, and most survived for several months. One of these monkeys remains alive today, now more than five years after replacement of the heart and both lungs.

With the encouraging experience in primate heart-lung allografts and a satisfactory clinical immunosuppressive regimen in cardiac allografts based on cyclosporine, it seemed that a clinical trial of combined heart and lung transplantation in humans would at last be appropriate. This was begun in March 1981.

The world's fourth heart-lung transplant was carried out at Stanford in March 1981 and the patient, a 45-year-old woman with primary pulmonary hypertension, remains alive and well 4½ years later. A total of 26 patients have now undergone 27 combined heart-lung transplants in the Stanford series, with a one-year survival of about 70%. All recipients

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presented with end-stage pulmonary hypertension, either as a consequence of Eisenmenger's syndrome or of primary pulmonary hypertension. Total survival after combined heart-lung transplantation is now more than 400 patient-months.

Transplant Recipients

There are obviously many patients who might benefit from combined heart and lung transplantation, and they can be broadly divided into those who have damage of both the heart and lungs, or those who have irreversible pulmonary failure alone. The first category comprises patients with advanced pulmonary vascular disease—either Eisenmenger's syndrome or primary pulmonary hypertension.

The current medical treatment of patients with Eisenmenger's syndrome is symptomatic only and limited to the management of cardiac failure, hemoptysis, polycythemia and its complications and the avoidance of pregnancy. Conventional surgical operations for patients with Eisenmenger's syndrome are contraindicated because closure of the defect after the development of irreversible pulmonary hypertension will lead to right-sided heart failure and death. Similarly, cardiac transplantation alone would fail because the fixed and elevated pulmonary vascular resistance would result in acute right-sided failure of a normal donor heart. Combined heart and lung transplantation is the only potentially curative therapy for patients with this condition.

Primary pulmonary hypertension is a disease that mainly afflicts young women and, though it may be preceded by a viral illness or pregnancy, is often unheralded. This is a particularly distressing disease with a progressive and fatal course, afflicting as it does young persons often with young families. Medical therapy is limited to vasoactive drugs and calcium blocking agents, which at best provide temporary palliation. The heart shows gross right ventricular hypertrophy, and tricuspid regurgitation occurs as a result of right ventricular distension. Death finally occurs from hypoxia, ventricular arrhythmias or right ventricular infarction. Again, heart and lung transplantation is the only possible cure.

The second category of potential recipients for combined heart and lung transplantation consists of those with irreversible disease of both lungs without significant cardiac involvement. Included here are patients who have severe chronic obstructive airways disease, pulmonary fibrosis, cystic fibrosis and other enzyme deficiencies. Transplantation of the heart and the lungs is justified for many reasons. The results of heart and lung transplantation are superior to those for only lung transplantation. The combined operation in these patients also avoids the problems resulting from leaving one damaged lung in place, such as ventilation-perfusion defects and a reservoir of infection within the chest. Finally, our experience with cardiac transplantation guides immunosuppressive therapy because rejection of the heart and the lungs is often related.

At Stanford we have thus far restricted possible recipients to those who have pulmonary hypertension, either primary or the result of Eisenmenger's syndrome. This is because the shortage of suitable donors and the overwhelming number of possible recipients have forced us to transplant the patients we believe will do best. Those with pulmonary hypertension are good candidates because there is always significant cardiac involvement even in the primary form of this disease, and the patients are relatively young. In addition, the tracheobronchial tree is generally sterile, other organ involvement is usually the result of cardiac failure only (unlike, for example, with cystic fibrosis) and there is little likelihood of recurrence of the original disease in the transplanted organs.

However, the presence of adhesions from a previous cardiac surgical procedure (common in those with Eisenmenger's syndrome) increases the risk of the operation. Postoperative bleeding exacerbated by coagulopathy from hepatic congestion, multiple vascular bronchial anastomotic channels and adhesions and prolonged cardiopulmonary bypass times contributed to most of the early deaths. Similarly, a history of pulmonary emboli is a contraindication to the operation not only because of the possibility of recurrence but also because of the likelihood of severe adhesions at the site of previous infarcted areas.

Donors

Donors are the limiting factor in all transplant programs; the scarcity of donors is magnified for heart-lung transplantation, however. Brain death may be accompanied by neurogenic pulmonary edema, thoracic trauma or aspiration of gastric contents and prolonged ventilatory support may result in a tracheobronchial infection. Only about 10% of possible cardiac donors have lungs suitable for combined heart-lung transplantation.

Possible donors should be younger than 35 years, and ABO blood group compatibility and a negative crossmatch between recipient serum and donor lymphocytes are required. Obviously there should be an absence of preexisting heart or lung disease, a close size match and a completely clear chest on x-ray film. Slightly abnormal roentgenographic appearances indicate much greater pathology, which may be related to trauma or infection. It is important to ensure satisfactory myocardial function with an adequate blood pressure without high-dose inotropic support. Satisfactory gas exchange must also be evident, with an arterial partial oxygen pressure of more than 100 torr with a forced inspiratory oxygen of 40%, peak inspiratory pressures of less than 30 torr with normal tidal volumes and an absence of infected pulmonary secretions.

Size similarity between the transplanted lungs and the recipient's thoracic cage is obviously important for generating satisfactory tidal volumes, and it seems clear that in donor lungs that must be compressed to fit within the recipient thoracic cage significant atelectasis and pulmonary shunting would develop. A mismatch in the opposite direction involving the transplantation of small donor lungs into a large thoracic cavity is unlikely to be as detrimental because the lung has the capacity to expand considerably, as is often seen, for example, after a lobectomy. On our recipient list, we maintain patients of all sizes and blood groups to ensure that a suitable donor would always be used.

The Operation

The operation results in an almost incredible alteration in the physiologic status of the lung. The lungs are denervated and lack a cough reflex below the tracheal suture line, in addition to the loss of pulmonary afferent nerves. Disruption

of lymphatic drainage and loss of the bronchial arterial supply are also consequences of the operation; lymphatic continuity becomes restored after a few weeks and only requires strict avoidance of fluid overload until this time; loss of the bronchial arterial supply appears to be without consequences. This is probably because there is adequate collateral supply from the coronary circulation, also transplanted in the combined operation.

The key to the operation is to remove the recipient's heart and lungs without injury to the surrounding nerves or loss of hemostasis. The heart-lung block is intimately related to important nerves traversing the thorax. The vagi lie immediately behind the pulmonary hilum on each side, anterior to the esophagus. The phrenic nerves are anterior to the hilum on each side, the right closer to the hilum than the left. The left recurrent nerve passes around the ligamentum arteriosum posterior to the pulmonary arterial bifurcation. The integrity of phrenic and recurrent laryngeal nerves is particularly important in these patients with denervated lungs, in order to sustain mechanical ventilation and coughing postoperatively.

Meticulous hemostasis with respect to the recipient's bronchial arterial circulation is essential, particularly in patients with Eisenmenger's syndrome, in whom these vessels are especially large and delicate. The size, friability and relative inaccessibility of these vessels after implantation of the graft make their prior control vital. Removing the heart and lungs separately aids visualization of the nerves and vessels and is an important part of the operative technique.[14]

Implanting the donor organs requires only the anastomosis of the trachea, right atrium and aorta.

The important features of the immediate postoperative care consist of administering immunosuppression, avoiding high inspired oxygen concentrations and instituting aggressive diuresis—the last being important because the lung has lost lymphatic drainage. The endotracheal tube is removed as early as possible, usually on the first postoperative day. Thereafter, because pulmonary secretions do not excite coughing, the patient is encouraged to cough frequently and to breathe deeply. Frequent postural percussion physiotherapy is vital for the first two weeks.

All patients receive cyclosporine as the basis of their immunosuppressive therapy. This is regulated by measuring serum cyclosporine concentrations. Many patients require very small doses of cyclosporine because of substantial hepatic impairment as a result of tricuspid regurgitation and hepatic congestion and cirrhosis. This impairment is accentuated by cyclosporine, which is both hepatotoxic and renal toxic. The use of steroids is avoided for two weeks to allow tracheal healing. Cyclosporine immunosuppression is therefore augmented for the first two weeks with azathioprine administration and an initial three- or four-day course of rabbit antithymocyte globulin given intramuscularly. After two weeks azathioprine is replaced with orally given prednisone at a dosage of 0.2 mg per kg of body weight per day.

Loss of Pulmonary Connections

These patients are, of course, the first humans in whom both lungs have been totally denervated and are therefore of interest in the study of the neural control of respiration. A recipient is immediately and probably permanently subjected to altered methods of regulation of breathing, but breathing patterns have in most cases been normal. The absence of nervous control of respiration thus appears not to be important in humans in either the short or the long term. Regulation of breathing apparently takes place through chest wall afferent nerves, carotid body receptors, circulating catecholamines and a central mechanism of rhythmic control of breathing. The rate and rhythm of breathing are not usually affected by altering inspired gas concentrations. During exercise, when studied four months postoperatively, appropriate increases in minute volume, tidal volume and respiratory rate occur. Blood gas values remain normal. It is unlikely that reinnervation of the lungs is ever accomplished; certainly cardiac reinnervation has never been documented in heart transplant patients.

The healing of the airway anastomosis has been of major concern in lung transplantation, and, as mentioned above, unilateral lung transplantation has been marked by bronchial dehiscence. In single-lung transplantation, of course, there can be no oxygenated blood supply from the donor side of the airway, but here combined heart-lung transplantation gives a distinct advantage because in the latter operation coronary-bronchial collaterals can open up to restore vascularity to the vessels previously supplied by the bronchial arteries. Shortly after the operation has been completed, arterial bleeding can be seen from the cut surfaces of the donor pleural reflections and the donor trachea.

The loss of pulmonary lymphatic connections results in a tendency for pulmonary edema to develop during the first three weeks after transplantation, and an aggressive diuresis is maintained during this period with the aim of achieving a negative weight balance early postoperatively. This aggressive diuresis, of course, combined with the immediate effects of a fairly prolonged period of cardiopulmonary bypass and the necessity of cyclosporine administration, often necessitates temporary hemodialysis with ultrafiltration early postoperatively. Experimental and clinical evidence indicates that lymphatic regeneration occurs about three weeks after the operation.

Rejection

For some time we assumed that significant pulmonary rejection would not occur without some evidence of cardiac rejection on cardiac biopsy. This working hypothesis was based on early experimental findings in dogs and primates. It has now been shown in monkeys, however,[15] and confirmed in two humans,[16] that this is not invariably the case. Positive findings on cardiac biopsy, therefore, will always require treatment, but negative findings do not necessarily mean that there is no pulmonary rejection. There is currently no entirely satisfactory noninvasive technique for diagnosing lung rejection; chest roentgenography displays diffuse opacification but this may be confused with fluid overload or infection.

The diagnosis of pulmonary rejection in the first few weeks, then, is made by the presence of diffuse opacity radiologically when infection and fluid overload have been ruled out. High temperatures and leucocytosis (possibly with eosinophilia) are characteristic.

Late Results

The 18 patients in the Stanford series who were discharged from hospital had normal exercise tolerance and

normal gas exchange four weeks after their operations.[17] Cardiac catheterization has been done in 13 patients after one year and in 5 after two years. In all, normal hemodynamics, including pulmonary artery pressures and pulmonary vascular resistances, were found. Coronary arteriograms were normal in these patients apart from the development of coronary collateral vessels to the area of the tracheal anastomosis. One of two patients studied at three years showed three-vessel coronary artery disease and increased pulmonary artery pressure as a result of recurrent pulmonary vascular disease; both the pulmonary and coronary vascular diseases were probably a result of immune-mediated injury. This patient had repeat transplantation and has since left hospital, having recovered fully from his second combined transplantation procedure.

There have been three late deaths—at 11, 14 and 15 months—where respiratory failure played a significant part. In six of the long-term survivors, including the three who died, late pulmonary complications have developed. Symptoms have included progressive breathlessness and cough (often productive) with or without a fever, with signs of diffuse crepitations and expiratory rhonchi. Serial pulmonary function tests have shown obstructive airway physiology in all six patients with superimposed restriction in three. On histologic examination of tissue from open-lung biopsy or autopsy, there was obliterative bronchiolitis in five of these six patients.[18] This syndrome has been unresponsive to treatment with antibiotics, bronchodilators or active physiotherapy. A regimen of corticosteroids was given in four patients late in the course of their deterioration but no sustained response was obtained. Three of these six patients are still alive: one continues to be dyspneic on moderate exertion, one has undergone successful retransplantation and one awaits retransplantation.

This late dyspnea is probably a consequence of rejection. It appears that late pulmonary rejection follows a far more insidious course than early rejection, and that irreversible damage can occur through the development of bronchiolitis obliterans and pulmonary vascular disease. Of course, in a nontransplanted lung, obliterative bronchiolitis is the histologic manifestation of pulmonary injury caused by a variety of factors, including viral infestation. Because a transplanted lung is particularly at risk for infection and other injury, it may be overly facile to ascribe these changes only to rejection.

The development of pulmonary vascular disease is interesting. Progressive vascular intimal proliferation tends to develop in all transplanted organs, which is probably the result of antibody-mediated immune injury to the endothelium. This has not been previously described in the lung, however, partly because until recently there have been no long-term survivors either in the laboratory or in the clinical situation. It was our hope that the lung might be free of this complication because of its low perfusion pressure. However, the development of pulmonary vascular disease has now been documented both in our experimental animals and in patients and, as mentioned above, has necessitated retransplantation in one recipient. It is somewhat ironic that a complication of the cure (transplantation) is a recurrence of the original condition, but clinically significant pulmonary hypertension has been seen in only one patient thus far and may be supposed to be the exception rather than the rule.

Though the development of late respiratory dysfunction in some of the recipients is worrisome, there is some evidence to suggest that this is the result of inadequate immunosuppression and thus may be avoided in the future. A seventh patient presented recently with this syndrome of cough, dyspnea on exertion and obstructive airway physiology, and early augmented immunosuppression resulted in the resolution of symptoms and a return to normal pulmonary physiology on pulmonary function testing.

Despite these complications in a minority of patients, most recipients have been free of late complications and the remaining 13 patients are fully rehabilitated and able to enjoy the life-style of their choice. This has indeed been remarkable in those with Eisenmenger's syndrome, born severely incapacitated and never having been able to exercise normally.

Conclusion

The recent results of combined heart-lung transplantation are considerably better than those for single-lung transplantation, where there are currently only two long-term survivors. The main advantage of the combined operation is the removal of all diseased tissue, thus avoiding recurrent infection and ventilation-perfusion imbalance from the remaining lung. In addition, it is likely that the presence of coronary-bronchial vascular collateral channels, shown at coronary arteriography in these patients, aids tracheal healing. Neither early nor late complications have been seen from the tracheal anastomosis after heart-lung transplantation in the Stanford series, which is in sharp contradistinction to the experience after single-lung transplantation.

The most significant practical problem in the administration of this procedure is the lack of availability of suitable donors. Pneumonic changes occur early in patients with brain death as a result of aspiration, infection or both, compounded by a tendency towards neurogenic pulmonary edema. Satisfactory preservation and storage of the heart-lung block have not yet been achieved and it remains necessary to transfer the donor to the recipient hospital for the removal of the heart and lungs. Although this may result in logistic difficulties, donors with normal lung function are so rare that consideration should always be given to heart-lung donation as a priority. Patients in end-stage pulmonary failure have no temporary support such as dialysis if the condition becomes terminal and heart-lung transplantation in no way precludes the use of other organs for donation.

There are many patients with pulmonary failure apart from those with pulmonary hypertension who could benefit from combined heart-lung transplantation. We have not yet transplanted patients with end-stage parenchymal disease because of the shortage of donors and the overwhelming surfeit of suitable recipients. Advances in the understanding, diagnosis and treatment of lung rejection are likely to make this procedure a realistic therapy for many patients with pulmonary failure, especially when the understanding of lung preservation allows improved donor procurement and those physicians caring for brain-dead patients are aware of the tremendous potential for the relief of pain and suffering that transplantation can provide.

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Overview of Marrow Transplantation

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Bone marrow transplantation is now an accepted form of therapy for many hematologic disorders including aplastic anemia, genetically determined diseases and malignant diseases, particularly leukemia, and for rescue of patients given intensive chemoradiotherapy for malignant disease. The donor may be a healthy identical twin, a family member or even an unrelated person. Selection is made on the basis of human leukocyte antigen tissue typing. Intensive chemoradiotherapy is used to suppress patients' immune systems to facilitate engraftment and destroy diseased marrow. Transfusion of platelets, erythrocytes and granulocytes (or all of these), antibiotic coverage and protection from infection are necessary during the pancytopenic period. Use of a Hickman catheter facilitates maintenance of adequate nutritional intake and provides easy access for drawing blood and intravenous administration.

Survival rates vary considerably depending on a patient's disease, clinical state and age. Patients with aplastic anemia transplanted early in the course of their disease have a survival rate of approximately 80%. Patients with acute lymphoblastic leukemia are usually transplanted in a second or subsequent remission and have a survival rate of 25% to 40%. Patients with acute nonlymphoblastic leukemia in remission have survivals ranging from 45% to 70%. More than 200 patients in the chronic phase of chronic granulocytic leukemia have been transplanted with survival ranging from 50% to 70%. Complications of marrow transplantation include marrow graft rejection, graft-versus-host disease, immunologic insufficiency and the possibility of recurrence of the leukemia. The risk of death from these complications must be balanced against the possibility of cure.

(Thomas ED: Overview of marrow transplantation, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:834-837)

The bone marrow, widely scattered in the medullary cavities, is an organ roughly the size of the liver. It is a busy organ, producing the short-lived circulating blood cells and playing a major role in immunologic and macrophage functions. The marrow is susceptible to a variety of diseases and its function may be impaired by treatment of other diseases, particularly cancer. Destruction of diseased marrow or replacement of damaged marrow by marrow transplantation was first shown in studies in animals. Attempts at clinical applications of marrow transplantation, begun in the 1950s, were largely unsuccessful until the end of the 1960s when supportive care techniques, improved antibiotics and knowledge of human histocompatibility typing ushered in the "modern" era of marrow transplantation. Marrow grafts are now carried out for aplastic anemia, a form of organ failure, for genetically determined diseases—both immunologic deficiency diseases and hematopoietic diseases—for malignant diseases, principally the leukemias, and for replacing a patient's normal marrow damaged by intensive chemoradiotherapy for malignant disease.

Donor Selection

A donor may be a healthy identical twin—a syngeneic graft—or a family member or an unrelated person—an allogeneic graft. Under appropriate circumstances, the patient's own marrow may be used—an autologous graft. To the present time most allogeneic grafts have used a human leukocyte antigen (HLA)-identical brother or sister as the donor. HLA, the major histocompatibility complex in humans, is governed by a region on chromosome 6, referred to as a haplotype. A person has two haplotypes, one inherited from each parent. Within a family, there is one chance in four that siblings will inherit the same combination of the two haplotypes. Such an "HLA-matched" normal sibling could then serve as donor for the patient. The marrow donation consists of multiple aspirations, mainly on the posterior iliac crest,

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and the principal risk for a donor is that associated with the necessary general or spinal anesthesia. The marrow is collected in an anticoagulant, screened to break up particles and given to the recipient by intravenous infusion.

Preparation of a Patient

Most patients require intensive chemoradiotherapy in preparation for engraftment to suppress the immune system so that a marrow graft can be accepted and to destroy diseased marrow whether the disease is a malignant one (leukemia) or is genetically determined. Patients with severe combined immunologic deficiency are immunosuppressed because of their disease and may accept an allogeneic graft without preparation.

Supportive Care

After the preparative regimen and infusion of marrow from the donor, two to four weeks are required before the marrow graft begins to function. During that time the patient has no functioning marrow and must be supported by transfusions of platelets, erythrocytes or granulocytes (or all of these), protected from infection by isolation techniques or prophylactic antibiotics and treated promptly for proved or suspected infection. Most patients now have a central venous double-lumen Hickman catheter installed to facilitate hyperalimentation, the administration of medication and blood products and for the simplified drawing of blood specimens.

Engraftment

Rising granulocyte and platelet counts and the reappearance of reticulocytes indicate engraftment. The regenerating marrow is usually entirely of donor type confirmed by the use of cytogenetics, blood genetic markers or restriction enzyme fragment-length polymorphisms.

Clinical Results of Marrow Transplantation

Aplastic Anemia

Aplastic anemia, usually of unknown cause (idiopathic) but sometimes due to drugs, insecticides or other chemical agents, may be considered a form of organ failure. The problem is to replace the failed organ with normally functioning marrow from the donor. The most widely used immunosuppressive regimen is cyclophosphamide, 50 mg per kg of body weight on each of four days, followed 36 hours later by donor marrow. The first two successful transplants were carried out in 1971 and both recipients are alive and well 14 years later.

For ethical reasons the initial marrow transplants were carried out in patients who had already received multiple transfusions and who were severely infected at the time of transplantation. A third of the patients had graft rejection, and the long-term survival of these end-stage patients was 40% to 50%. Blood transfusions may sensitize an intended marrow transplant recipient to minor non-HLA antigens present in the donor but not the recipient, resulting in rejection of the marrow graft. Patients with severe aplastic anemia identified early in the course of the disease before blood transfusions were given usually do not reject the marrow graft. The long-term survival of these patients is about 80%. Therefore, patients with severe aplastic anemia and their families should have tissue typing done immediately after diagnosis. If a suitable donor can be identified, marrow transplantation should be carried out promptly before transfusions become necessary.

Many patients with severe aplastic anemia, however, require transfusions because of bleeding, infection or both. Therefore, other preparative regimens designed to prevent graft rejection and to improve survival have been developed. These include administering procarbazine hydrochloride and antithymocyte globulin before the standard cyclophosphamide regimen or a cyclophosphamide regimen followed by total-body irradiation of 8 gray with shielding of the lung to 4 gray. Because it is not practical to get more marrow cells from the donor, the Seattle team has used peripheral blood mononuclear cells as an added source of donor cells. Following the usual cyclophosphamide regimen and the marrow transplant, buffy-coat leukocytes were collected from 4 units of donor blood by a leukapheresis technique and administered intravenously to the recipient without in vitro irradiation for three to five days after the transplant. For patients who have been transfused, these regimens have largely solved the problem of graft rejection, and long-term survival has ranged from 50% to 75%.

Acute Leukemia

Acute leukemia has served as a prototypical malignant disease for treatment by intensive chemoradiotherapy and marrow transplantation. Almost all regimens for preparing leukemic patients for marrow transplantation have used supralethal total-body irradiation because irradiation is an effective means of eradicating leukemic cells, it penetrates to the so-called privileged sites where leukemic cells may be inaccessible to chemotherapeutic agents and it is a powerful immunosuppressive agent.

Transplantation for Acute Leukemia in Relapse Using HLA-Identical Sibling Donors

Marrow transplantation was initially carried out only in patients with acute leukemia in relapse after combination chemotherapy. These end-stage patients were poor candidates for any therapeutic procedure. The Seattle team used a regimen of cyclophosphamide, 60 mg per kg on each of two days, followed by 10 gray (1,000 rads) total-body irradiation and the marrow transplant. There were many deaths related to advanced illness at the time of transplantation, graft-versus-host disease, opportunistic infections or recurrence of leukemia. Only 10% of these patients are long-term survivors, with the leading patients now 14 years postgrafting. These patients, who are receiving no maintenance chemotherapy, are apparently cured of their disease. The fact that some of these patients in the end stage of their disorder could be cured was encouraging.

Transplantation for Acute Lymphoblastic Leukemia in Remission Using HLA-Identical Sibling Donors

Some cures of end-stage disorders led to transplantation earlier in a disease course. Many patients with acute lymphoblastic leukemia, particularly children in the the "good-risk" category, can be cured by combination chemotherapy, but once marrow relapse occurs, long-term survival is rare. Therefore, the decision was made to transplant patients in a second or subsequent remission. Most marrow transplant teams are reporting long-term survival and apparent cure in

25% to 40% of these patients. Recurrent leukemia is a major problem showing that the preparative regimen was often ineffective in eradicating the residual leukemic cell population.

Transplantation for Acute Nonlymphoblastic Leukemia in Remission Using HLA-Identical Sibling Donors

In contrast to patients with acute lymphoblastic leukemia, those with acute nonlymphoblastic leukemia in first remission are known to have a poor prognosis because only about 20% of the patients are alive at five years after initial chemotherapy. Therefore, a study of marrow transplantation in these patients was considered to be ethically acceptable. In the initial series of 22 patients transplanted in first remission, 12 (55%) continue to be in disease-free remission now six to nine years after grafting. Several hundred such transplants have now been carried out with various marrow transplant teams reporting 45% to 70% long-term survival.

Marrow Transplantation for Patients With Chronic Granulocytic Leukemia

The term "chronic" is misleading in describing the clinical course of patients with chronic granulocytic leukemia because the median survival in most series of patients is about 30 to 50 months. When the blast crisis of the disease appears, therapy is usually ineffective, although some patients may respond for a period of a few months to treatment with vincristine and prednisone. Marrow transplantation from HLA-identical donors has been carried out in patients with chronic granulocytic leukemia in blast crisis. Between 10% and 20% of these patients are long-term survivors without the Philadelphia chromosome and appear to be cured.

The Seattle team has used marrow transplantation during the chronic phase of the disease for 16 patients with an identical twin to serve as marrow donor. One patient died early and four relapsed, one of whom died of leukemia at 51 months. The other patients are clinically and cytogenetically normal one to nine years after transplantation. These results of syngeneic marrow transplantation indicate that the Philadelphia chromosome-positive leukemic clone could be eliminated and suggest that marrow transplantation in the chronic phase of chronic granulocytic leukemia should be effective when using allogeneic donors. Seven marrow transplant teams have now reported HLA-identical grafts in about 200 patients in the chronic phase of chronic granulocytic leukemia. Long-term survival ranges from 50% to 70% and the absence of the Philadelphia chromosome indicates cure for most of these patients.

Immunologic Aspects of Marrow Transplantation

Marrow Graft Rejection

"Marrow graft rejection" describes a phenomenon in which the transplanted marrow graft begins to function but, after a few days or weeks, the peripheral blood counts suddenly drop and a marrow biopsy specimen shows the marrow to be devoid of myeloid elements. With a solid organ, such as the kidney, histologic proof of graft rejection is easily obtained, but such proof usually cannot be obtained with a marrow graft. Immunologically mediated marrow graft rejection is usually a consequence of sensitization by transfusions. Marrow graft failure may be due to causes other than immunologic mechanisms, such as (1) a defective or inadequate number of "stem cells" in the donor marrow; (2) a defective microenvironment in the marrow recipient; (3) allogeneic resistance not associated with HLA, and (4) susceptibility of the donor marrow to the same etiologic mechanism(s) responsible for the original disease process.

Acute Graft-Versus-Host Disease

A "wasting disease" or "runt disease" was described many years ago in newborn mice or in rodents exposed to lethal total-body irradiation and given infusions of allogeneic hematopoietic cells. The "disease" was recognized to be due to an immunologic reaction of engrafted lymphoid cells, presumably T cells, against the tissue of the host. This graft-versus-host reaction and its consequences, graft-versus-host disease, is a major complication of marrow transplantation in humans. In approximately two thirds of patients given a marrow graft from an HLA-identical sibling and postgrafting immunosuppression, minimal or more severe acute graft-versus-host disease will develop 10 to 80 days (median 33 days) after grafting. A skin rash is usually the first sign of graft-versus-host disease. Intestinal involvement results in diarrhea. Liver disease is characterized by abnormal liver function test values. Severe immunologic deficiency accompanies graft-versus-host disease, and death from infection is frequent.

Because graft-versus-host disease is immunologically mediated, efforts to prevent its development involve immunosuppressive therapy. The standard Seattle regimen consists of giving methotrexate, 15 mg per m^2 of body surface on day 1 postgrafting and 10 mg per m^2 on days 3, 6, 11, 18 and weekly thereafter through day 102. Despite this regimen, acute graft-versus-host disease of grade II (two or more organ systems) or greater severity will develop in 40% to 50% of patients.

A new drug, cyclosporine, is a potent immunosuppressive agent. It is particularly valuable in organ grafts such as kidney, heart and liver. Randomized trials have been carried out to compare the use of cyclosporine with that of methotrexate post grafting for their effectiveness in preventing acute graft-versus-host disease. These trials have not shown a difference in survival between the two regimens. Cyclosporine is useful, however, because it does not cause mucositis as methotrexate does, and it does not suppress the marrow graft so that effective marrow function is evident about one week earlier. Cyclosporine is nephrotoxic and marrow graft recipients often receive other nephrotoxic agents such as amphotericin for suspected fungal infection. The serum creatinine level and serum cyclosporine concentration must be monitored carefully, with prompt reduction of dosage if renal function is threatened.

The results of treatment of established acute graft-versus-host disease are unsatisfactory. In clinical trials, without untreated controls because of ethical considerations, prednisone, horse antithymocyte globulin and cyclosporine gave equivalent results with a good response in only about a third of the patients. Of the patients in whom moderate to severe graft-versus-host disease develops, about a third die with this disorder or its infectious complications. New approaches for preventing or treating acute graft-versus-host disease must be found.

Experiments are under way that are designed to eliminate from the marrow inoculum the T cells believed to be responsible for graft-versus-host disease while retaining hematopoi-

etic stem cells. Monoclonal antibodies that react with human T cells or subsets of T cells are being used in conjunction with complement or bound to toxins, such as the A chain of ricin, to create an immunotoxin. The preliminary results of these studies indicate a reduction in the incidence and severity of graft-versus-host disease. However, the incidence of graft failure is significantly increased. The mechanism of the graft failure is under investigation.

Chronic Graft-Versus-Host Disease

Chronic graft-versus-host disease occurs in about a fourth of those recipients who survive beyond 100 days after a marrow graft from an HLA-identical sibling. The manifestations include scleroderma-like skin disease, keratoconjunctivitis, buccal mucositis, esophageal strictures, small- and large-intestinal involvement, pulmonary insufficiency, chronic liver disease and generalized wasting. Chronic graft-versus-host disease may be associated with recurrent and occasionally fatal bacterial infections. Treatment with prednisone and either procarbazine, cyclophosphamide or azathioprine results in recovery of about 80% of the patients, although treatment may be required for one or even two years. The other 20% of patients continue to have problems that may be disabling.

Recovery of Immunologic Function

In the first months after grafting, allogeneic marrow graft recipients are susceptible to a wide variety of infections that may be due to pathogens or opportunistic agents that rarely cause disease in normal persons. In about a third of patients, an interstitial pneumonia develops and cytomegalovirus can be shown in about half of these cases. The prophylactic use of trimethoprim-sulfamethoxazole has virtually eliminated *Pneumocystis carinii* infection. The high incidence of infection is the result of a very slow return of immunologic function, which may be made worse by graft-versus-host disease and by efforts to prevent or treat it. In most patients herpes zoster develops, requiring treatment with acyclovir only if dissemination occurs. By the end of the first year after grafting, most patients have recovered immunologically and are able to lead normal lives without an increased incidence of infection. Regardless of the time after grafting, the patient and the physician must be alert for the symptoms and signs of infection to facilitate early diagnosis and treatment.

The Effect of Age

The success of allogeneic marrow grafting is inversely proportional to the age of the recipient. The most apparent explanation for this difference is the increased incidence and severity of graft-versus-host disease in older patients. Most marrow transplant centers do not carry out the procedure in patients older than 50. Syngeneic transplants can be carried out regardless of age because the patients do not have graft-versus-host disease, although patients over the age of 50 do not tolerate intensive treatment as well as younger ones.

Recurrent Leukemia After Grafting

Frequency of Recurrence of Leukemia

Of patients with leukemia in whom transplantation is done during relapse or during second remission, approximately 35% would be cured while 65% would be destined to relapse—if other causes of death are not considered. Only about 25% of patients with acute nonlymphoblastic leukemia who receive transplants in first remission subsequently relapse. The lower incidence of recurrent leukemia for those patients transplanted in the first remission may be explained by a small number of residual leukemic cells at the time of transplant or by the possibility that the leukemic cells of patients in first remission may not yet have acquired resistance to therapeutic agents.

Nature of Recurrent Leukemia

Blood genetic markers, cytogenetic techniques and restriction enzyme fragment-length polymorphisms can be used to identify the donor or host origin of the leukemic cells in patients who relapse after marrow transplantation. In most patients the recurrent leukemia is in host-type cells. However, ten cases have now been reported in which the recurrent leukemic cells were shown to be of donor origin. The mechanism of donor-cell transformation is unknown.

Cost Effectiveness and Ethical Concerns

The treatment of diseases such as acute leukemia or thalassemia major is expensive whether by "conventional methods" or by marrow grafting. The cost of marrow transplantation has been reduced appreciably by transplantation earlier in the course of the disease when the patient is in relatively good condition. Concern about exposing a patient to the marrow transplant regimen and the risk of death in the first one to three months after grafting have limited the use of marrow transplantation. However, the better long-term survival after marrow transplantation compared with conventional therapy for several diseases and the cure of some diseases not cured by conventional therapy have reduced the ethical concern. Extension of this form of therapy to other malignant diseases (lymphomas, Hodgkin's disease, selected solid tumors) and to a variety of genetic disorders (thalassemia major, sickle cell disease, enzyme-deficiency diseases) is being reported and the current rapid rate of progress may soon make a much broader application of marrow grafting a reality.

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One Institution's Experience With Pancreas Transplantation

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The University of Minnesota has the largest experience with pancreas transplantation of any institution, with 130 cases since 1966, including 116 in 98 patients between July 1978 and June 1985. Currently, 30 patients are insulin-independent, 19 for greater than one year, the longest for seven years. One-year patient and graft survival rates overall are 87% and 30%, respectively. Of 98 recipients, 49 had had previous kidney transplants, while 49 had not, and currently most of the pancreas recipients do not have uremia and have not had a kidney transplant but have early complications of diabetes. A total of 44 of the grafts were procured from related and 72 from cadaver donors. Although 32 of the 116 grafts (28%) failed for technical reasons, the most common cause of graft failure has been rejection. Various immunosuppressive regimens have been used in attempts to reduce the rejection rate, and one combination, low-dose cyclosporine-azathioprine-prednisone (triple therapy), has been particularly effective, with a one-year functional survival rate of 73% in recipients of technically successful grafts from human leukocyte antigen-mismatched cadaver or related donors (N = 20). The pancreas graft survival rates have improved gradually (43% for 1984 to 1985, N = 30; versus 27% for 1978 to 1983, N = 86) for transplants from both related and cadaver donors. Metabolic studies from most recipients with functioning grafts (insulin-independent) show normal or nearly normal results. Preliminary observations on secondary complications suggest a more favorable course in recipients whose grafts have functioned long term than in those whose grafts failed early.

(Sutherland DER, Goetz FC, Kendall DM, et al: One institution's experience with pancreas transplantation, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:838-844)

Between December 16, 1966, and June 6, 1985, 130 pancreas transplants were carried out in two series at the University of Minnesota Medical School.[1] The second series, begun on July 25, 1978, comprises 116 pancreas transplants in 98 patients and has encompassed several changes in surgical technique, graft preservation, recipient immunosuppression and recipient and donor selection in an attempt to evolve an approach that would result in a high success rate. The various techniques, in a rough chronological and overlapping order, include leaving the duct open,[2] duct injection,[3] duct ligation,[4] ductoenterostomy[4] and ductocystostomy. Immunosuppressive regimens have included azathioprine and prednisone,[3] cyclosporine and prednisone[5] and cyclosporine, azathioprine and prednisone in combination.[1,6] Donors have been both cadavers and living relatives.[7-9] Initially, all recipients had previously had kidney transplants, while in recent years most recipients have had neither uremia nor a kidney transplant but have had early or only moderately advanced, but progressive, secondary complications. In this report, we summarize the results of an analysis of pancreas transplant outcome of our second series according to isolated factors and within various subcategories according to combinations of these factors.

Patients and Methods

From July 25, 1978, to June 6, 1985 (Figure 1), 116 pancreas transplants were carried out in 98 patients with diabetes mellitus—49 with previous kidney transplants for end-

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stage diabetic nephropathy, 49 without end-stage diabetic nephropathy—72 from cadaver donors—40 segmental, 32 whole-organ grafts[1,10]—and 44 (all segmental) from related donors—27 human leukocyte antigen (HLA)-identical siblings, of whom 6 were identical twins, 8 HLA-mismatched siblings, 8 parents and 1 cousin. In all, 14 patients received two pancreas transplants, and 4 of these received a third pancreas transplant after the previous grafts failed; all of the retransplants were from cadaver donors. Fifteen of the recipients had previously received kidneys from their related donors—seven HLA-identical siblings, seven mismatched relatives and one identical twin. At the time of primary pancreas transplantation, the patients—38 men, 60 women—ranged in age from 16 to 52 years (mean ± standard deviation of 32.5 ± 6.5 years). The age of onset of diabetes mellitus ranged from 1 to 30 years (mean, 9.9 ± 5.1 years). The duration of diabetes at the time of the pancreas transplant ranged from 10 to 40 years (mean, 22.6 ± 5.7 years). In the recipients who had previously had a kidney transplant, the interval from the kidney to the pancreas transplant ranged from 0.3 to 9.4 years (mean, 3.4 ± 2.3 years).

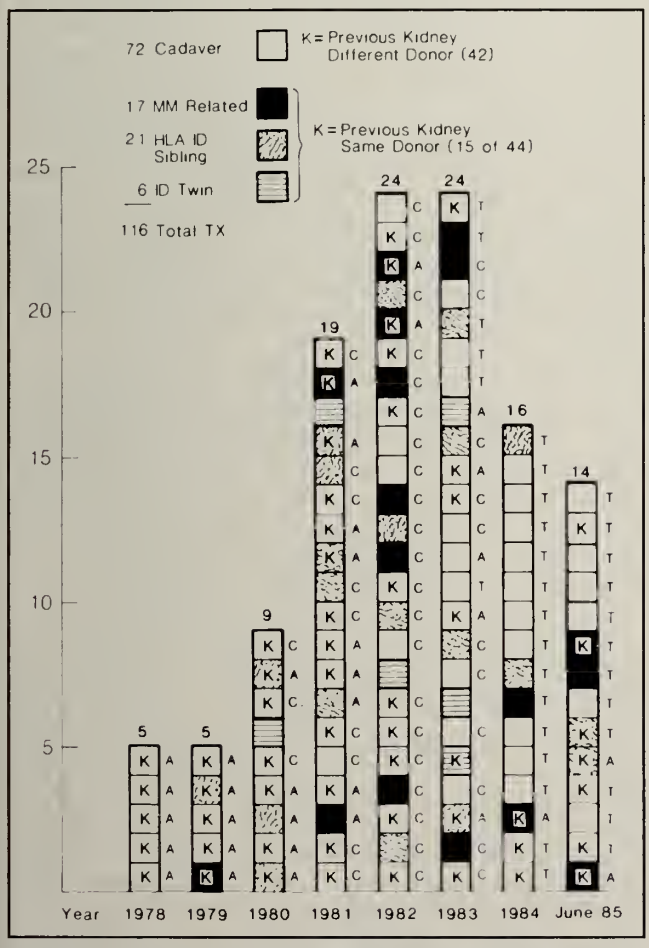

Figure 1.—Number of pancreas transplants by year at the University of Minnesota between July 25, 1978, and June 6, 1985, according to donor source and association with previous kidney transplants. In recipients of previous kidney grafts, the pancreas grafts of living related donors were from the same donor as the kidney with one exception, but those from cadavers were always from a donor different from that for the kidney. The letters to the right of each square indicate the drug regimen: A = azathioprine plus prednisone (N = 34), C = cyclosporine plus prednisone (N = 44), T = cyclosporine plus azathioprine plus prednisone (N = 33). HLA ID = human leukocyte antigen-identical, MM = [HLA] mismatched, TX = transplants

Of the cadaveric grafts, 26 were transplanted immediately after removal from the donor, and 45 were stored for 2 to 26 hours (mean, 11.0 ± 5.5 hours) at 4°C (1 in Collins' solution[2] and 45 in modified silica gel filtered plasma).[11] All but three grafts functioned immediately.[12]

Techniques for management of the exocrine secretion included open-duct intraperitoneal drainage in 15 (10 cadaver, 5 related), duct ligation in 3 (all cadaver), duct injection in 39 (34 cadaver, 5 related), ductoenterostomy in 57 (23 cadaver, 34 related) and ductocystostomy in 2 cases (both cadaver). Of the 32 whole pancreas transplants (all cadaver), 1 was open duct, 15 were duct injected, 14 were anastomosed to a Roux-en-Y limb of recipient jejunum (8 with a large duodenal patch encompassing both the papilla of Vater and the duct of Santorini; 6 of the papilla of Vater only) and 2 were anastomosed to the recipient's bladder. Of graft failures, 32 of the grafts—17 cadaver, 6 HLA-identical siblings (3 who were and 3 who were not previous kidney donors), 7 HLA-mismatched relatives (3 who were and 4 who were not previous kidney donors) and 2 identical twins—failed for technical reasons (1 bladder drained, 3 duct ligated, 3 duct injected, 8 open duct and 17 enteric drained).

Of the 80 recipients of technically successful allografts (55 cadaver, 15 HLA-identical and 10 nonidentical related), 18 (9 cadaver, all with previous kidneys from different donors; 4 HLA-identical siblings with a previous kidney from the same donor; 5 mismatched relatives, 4 with and 1 without previous kidneys from the same donor) were treated with azathioprine and prednisone as the principal immunosuppressants; 39 (28 cadaver, 19 with and 9 without previous kidneys; 8 HLA-identical siblings, and 3 mismatched relatives, none with previous kidneys) were treated with cyclosporine and prednisone as the principal immunosuppressants, and 23 (18 cadaver, 6 with and 12 without previous kidneys; 2 HLA-identical and 2 mismatched relatives without previous kidneys, and 1 HLA identical with a previous kidney from another HLA-identical sibling) were treated with a combination of cyclosporine, azathioprine and prednisone (triple therapy). Rejection episodes were treated with a transient increase in prednisone dose, a temporary course of antilymphocyte globulin or both.

Results

Currently (June 15, 1985), 78 of the 98 recipients are alive, and 30 have functioning grafts and are insulin-independent. Of the 30 patients, 1 has an open-duct graft at 6.9 years; 4 have duct-injected grafts at 2.1, 2.6, 2.8 and 4.5 years; 24 have enteric-drained grafts at less than 1 month (two patients), at 1 month (two patients), at 4 (two), at 5 (three), at 7, at 12 (two), at 13, at 15, at 16, at 18 (two), at 22, at 23 (two), at 28, at 31, at 41 and at 44 months, and 1 has a pancreaticocystostomy at 4 months posttransplant. In all, 27 grafts functioned for at least a year, including 19 of those currently functioning. Two recipients of open-duct grafts and one recipient of an enteric-drained graft began insulin injections for hyperglycemia between two and four years after transplantation, but had C-peptide levels above baseline and they are not prone to have ketosis. Three recipients of duct-injected grafts were insulin-independent for more than a year; one then had

rejection of the graft, while the other two died of cardiovascular disease at more than three years posttransplant, with still-functioning grafts. Two recipients of enteric-drained grafts had rejection of the pancreas transplants at 1.7 and 1.8 years posttransplant.

In the entire series of 116 grafts, losses attributed to technical causes occurred in 32 instances (28%) and to immunologic causes in 48 (41%) cases (44 probable rejection, 4 autoimmune recurrence of disease). Six patients died with functioning grafts.

For all cases, one-year actuarial patient and graft function (insulin-independent) survival rates were 86% and 30%, respectively (Figure 2-A). The survival rate has been significantly higher for recipients of grafts from related than from cadaver donors (95% versus 79% at one year, Figure 2-B). The functional survival rate of related donor grafts has exceeded that of cadaver donor grafts (41% versus 23% at one year) and has been higher for grafts from HLA-identical siblings than from HLA-mismatched relatives (46% versus 34% at one year, Figure 2-C). The benefit of HLA matching was most evident when only technically successful allografts were analyzed; in this subgroup, 76% of grafts from HLA-identical siblings, 58% from mismatched relatives and 30% from cadaver donors were functioning at one year (Figure 2-D).

The transplants from identical twin donors are in a separate category because the first three recipients of technically successful grafts were not immunosuppressed prophylactically and, in all three, hyperglycemia occurred between 6 and 12 weeks. On graft biopsy, this was associated with insulitis without evidence of rejection, thus representing an autoimmune recurrence of the original disease.[13] The process was partially reversed by administering antilymphocyte globulin and azathioprine in the third recipient, while the fourth recipient of an identical-twin pancreas graft was given azathioprine prophylactically beginning at the time of transplantation. The fourth identical twin graft recipient is currently insulin-independent at 1.9 years posttransplant.

Two categories of pancreas donors were associated with particularly high graft function survival rates: HLA-identical siblings and related donors who had previously given a kidney to the recipient, regardless of match. Conversely, the graft function survival rates of HLA-mismatched grafts from either related or cadaver donors in recipients who had not received kidney transplants, or in those who had previously received kidney transplants from a different donor than the pancreas, were low and similar. When all pancreas transplant cases were analyzed, the one-year functional survival rate for allografts from the same living donor as the previous kidney was 60%, while in those who had neither uremia nor a previous kidney transplant who were recipients of grafts from HLA-identical siblings it was 52%. Likewise, the one-year functional survival rate was 22% in recipients of HLA-mismatched grafts (cadaver and related) who had not had kidney transplants and 23% in recipients of cadaver pancreas grafts who had previously received a kidney from a different donor (Figure 3-A). The same analysis done for technically successful allografts alone showed that the one-year functional survival rate for grafts from the same living donor as the previous kidney (four HLA-identical siblings and four nonidentical related, all treated with azathioprine and prednisone) was 100%, and of grafts from HLA-identical siblings in nonuremic, nonkidney transplant patients (ten treated with cyclosporine and prednisone and two with triple therapy) it was 68%; for those who had neither uremia nor a kidney transplant and who received grafts from HLA-mismatched donors (21 cadaver and 6 related; 1 treated with azathioprine-prednisone, 12 with cyclosporine-prednisone, 14 with triple therapy) it was 33%, and for those with a previous kidney transplant who received cadaver pancreas grafts (9 treated with azathioprine-prednisone, 19 with cyclosporine-prednisone, 6 with triple therapy) it was 29% (Figure 3-B). Because until recently the rejection rate was low only in recipients of grafts from HLA-identical siblings or from previous related kidney donors, the influence of duct management techniques could be assessed only in this group of patients, and the highest functional survival rate has been obtained in grafts drained enterically (Figure 3-C).

In 1983 it became apparent that recipient immunosuppressive regimens of azathioprine and prednisone or cyclosporine and prednisone were associated with low functional survival rates for grafts from HLA-mismatched related or cadaver donors, and we began using cyclosporine, azathioprine and prednisone in combination (triple therapy). This change has been associated with improved results, and the one-year actuarial functional survival rate of technically successful grafts from HLA-mismatched donors is 73% in 20 recipients—6 with and 14 without previous cadaver kidneys; 18 cadaver and 2 mismatched related pancreas donors—treated with triple therapy, as compared with one-year graft survival rates of 20% in 10 azathioprine-prednisone and 13% in 31 cyclosporine-prednisone treated recipients of HLA-mismatched grafts (excluding those from a previous kidney donor) from our earlier experience (Figure 3-D).

In all, 32 recipients of technically successful grafts, 12 from related and 20 from cadaver donors, have been treated for rejection episodes as manifested by the occurrence of hyperglycemia several weeks or months after transplantation. Eleven recipients—six with related and five with cadaver donor grafts—reverted to euglycemia and are currently insulin-independent—a 34% response rate overall, 50% in the related-donor and 25% in the cadaver-donor category.

The changes we have made in surgical technique and in immunosuppressive protocols have been associated with a higher success rate of pancreas transplantation (Figure 4-A and B). For all cases, including technical failures, the one-year graft survival rate for transplants done between 1978 and 1983 was 27% (37% for related and 20% for cadaver donor pancreases), whereas for 1984 to 1985 it was 43% (67% for related and 31% for cadaver donor pancreases). Patient survival rates have been similar in both eras (Figure 4-C and D), 85% at one year for primary transplants done between 1978 and 1983—94% for recipients of related and 78% for recipients of cadaver donor grafts—and 88% for primary transplants done during 1984 and 1985—100% for recipients of related and 82% for recipients of cadaver donor grafts. Overall, patient survival rates have been similar in pancreas transplant recipients who have or have not had previous kidney transplants (Figure 5-A), but in each of these categories the patient survival rates were higher in recipients of related than of cadaver donor grafts (Figure 5-B and C).

Metabolic studies in the recipients with functioning grafts have shown that most are restored to a euglycemic state with

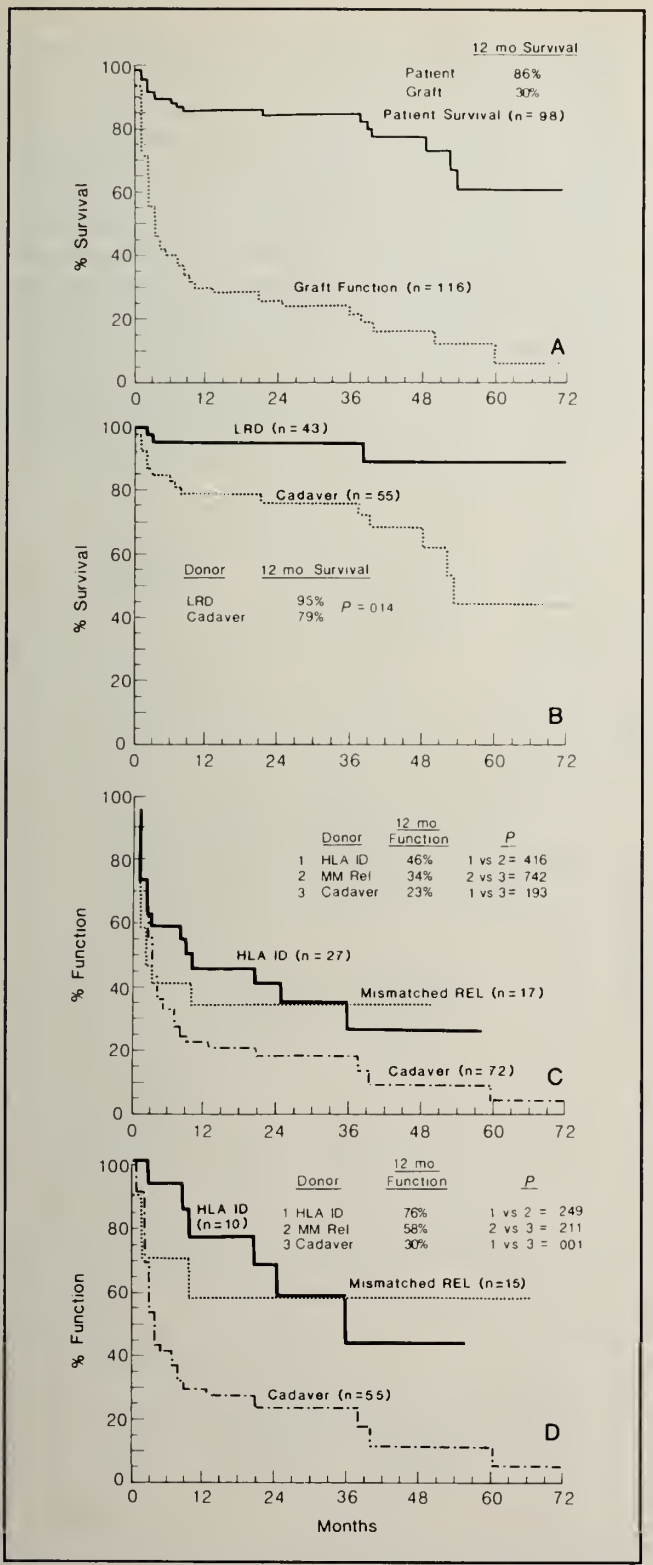
12 mo Survival
Patient 86%
Graft 30%
Patient Survival (n = 98)
Graft Function (n = 116)
% Survival
A
LRD (n = 43)
Cadaver (n = 55)
Donor 12 mo Survival
LRD 95%
Cadaver 79%
P = 014
B
% Function
Donor 12 mo Function P
1 HLA ID 46% 1 vs 2 = 416
2 MM Rel 34% 2 vs 3 = 742
3 Cadaver 23% 1 vs 3 = 193
HLA ID (n = 27)
Mismatched REL (n = 17)
Cadaver (n = 72)
C
HLA ID (n = 10)
Donor 12 mo Function P
1 HLA ID 76% 1 vs 2 = 249
2 MM Rel 58% 2 vs 3 = 211
3 Cadaver 30% 1 vs 3 = 001
Mismatched REL (n = 15)
Cadaver (n = 55)
D
Months

Figure 2.—A, Actuarial patient and graft functional survival rates as of June 15, 1985, for all pancreas transplant cases done at the University of Minnesota between July 25, 1978, and June 6, 1985. **B,** Patient survival rate for all recipients of primary grafts according to whether the donor was a living relative (LRD) or a cadaver. **C,** Pancreas graft functional survival rate according to donor source for all cases, including technical failures. **D,** Functional survival rate, according to donor source, of technically successful allografts only. HLA ID = human leukocyte antigen-identical, MM Rel = [HLA]-mismatched relative

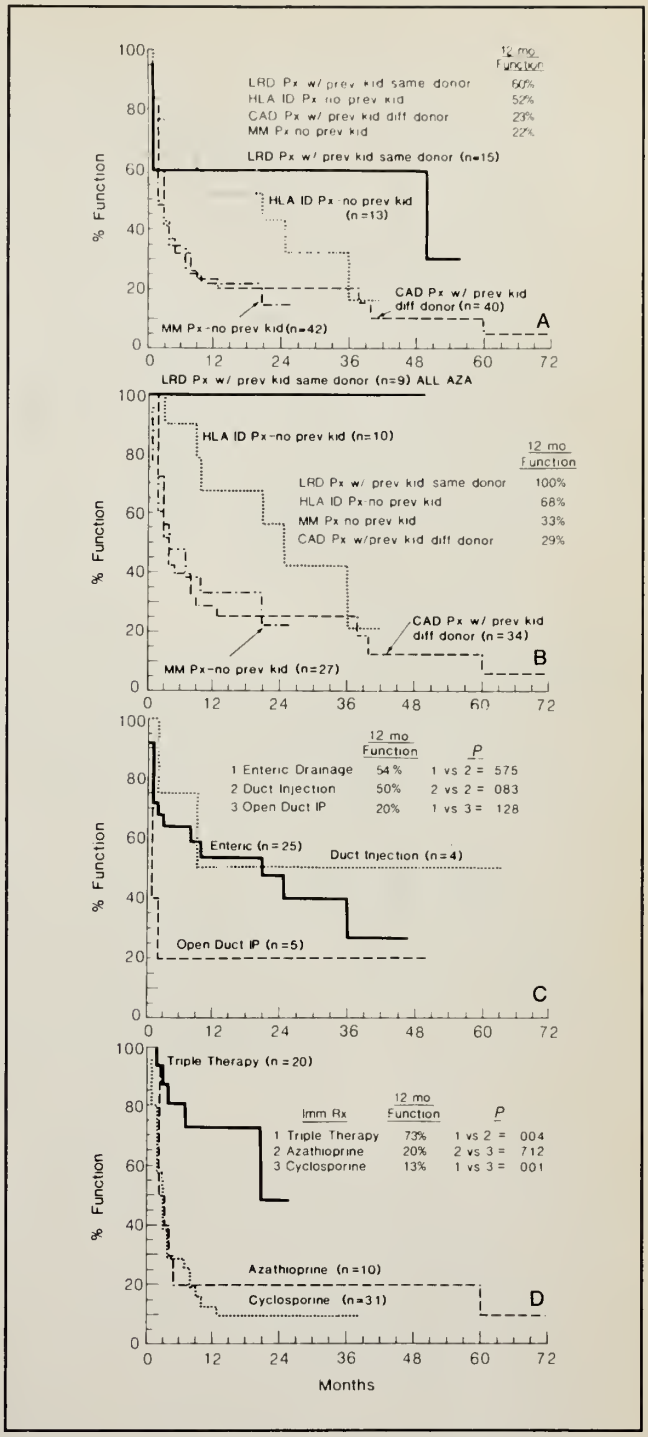
12 mo Function
LRD Px w/ prev kid same donor 60%
HLA ID Px no prev kid 52%
CAD Px w/ prev kid diff donor 23%
MM Px no prev kid 22%
LRD Px w/ prev kid same donor (n=15)
HLA ID Px-no prev kid (n=13)
CAD Px w/ prev kid diff donor (n=40)
MM Px-no prev kid (n=42)
% Function
A
LRD Px w/ prev kid same donor (n=9) ALL AZA
HLA ID Px-no prev kid (n=10)
12 mo Function
LRD Px w/ prev kid same donor 100%
HLA ID Px-no prev kid 68%
MM Px no prev kid 33%
CAD Px w/prev kid diff donor 29%
CAD Px w/ prev kid diff donor (n = 34)
MM Px-no prev kid (n=27)
B
12 mo Function P
1 Enteric Drainage 54% 1 vs 2 = 575
2 Duct Injection 50% 2 vs 3 = 083
3 Open Duct IP 20% 1 vs 3 = 128
Enteric (n = 25)
Duct Injection (n = 4)
Open Duct IP (n = 5)
C
Triple Therapy (n = 20)
Imm Rx 12 mo Function P
1 Triple Therapy 73% 1 vs 2 = 004
2 Azathioprine 20% 2 vs 3 = 712
3 Cyclosporine 13% 1 vs 3 = 001
Azathioprine (n = 10)
Cyclosporine (n = 31)
D
Months

Figure 3.—A, Pancreas graft functional survival rates for all cases according to four categories: pancreas grafts (Px) from the same living related donor (LRD) as a previous kidney (prev kid); human leukocyte antigen-identical (HLA ID) sibling grafts into patients who had neither uremia nor a previous kidney transplant; mismatched (MM) related or cadaver (CAD) grafts in recipients of previous kidney transplants from a different donor or in those with no previous kidney transplants. **B,** Same as **A** except only technically successful grafts were analyzed. All AZA = all received azathioprine **C,** Functional survival rates according to technique of grafts from HLA-identical sibling or of mismatched related donors of a previous kidney. IP = intraperitoneal [drainage] **D,** Functional survival rates according to immunosuppressive therapy (Imm Rx) in nonuremic recipients of HLA-mismatched grafts from cadaver donors or mismatched related donors who have not previously given a kidney.

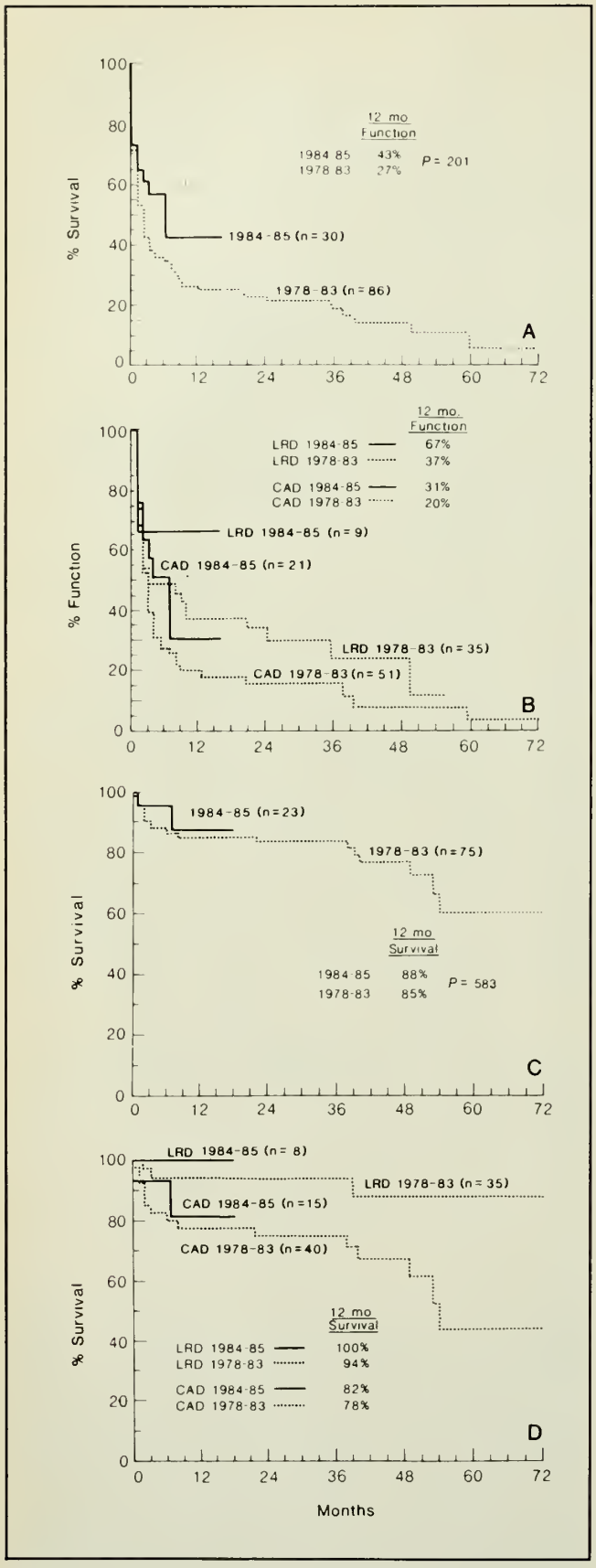

Figure 4.—Pancreas graft function survival rates **(A** and **B)** and recipient survival rates **(C** and **D)** according to year of transplant in all cases **(A** and **C)** and separately in recipients of transplants from either living related (LRD) or cadaver donors (CAD) **(B** and **D)**.

normal or nearly normal glucose tolerance test results.[1,14] The mean plasma glucose values before transplantation and during the latest 24-hour profiles and orally administered glucose tolerance tests done in 15 currently insulin-independent recipients whose grafts were functioning at one year and more are shown in Figure 6 and compared with the results obtained in normal persons. The mean plasma glucose levels in pancreas transplant recipients are within the normal range but tend to be on the high side. Some recipients have absolute euglycemia, whereas others who have functioning grafts and are insulin-independent have values that are definitely above the normal range, as reflected in the standard deviations from the mean for the entire group.

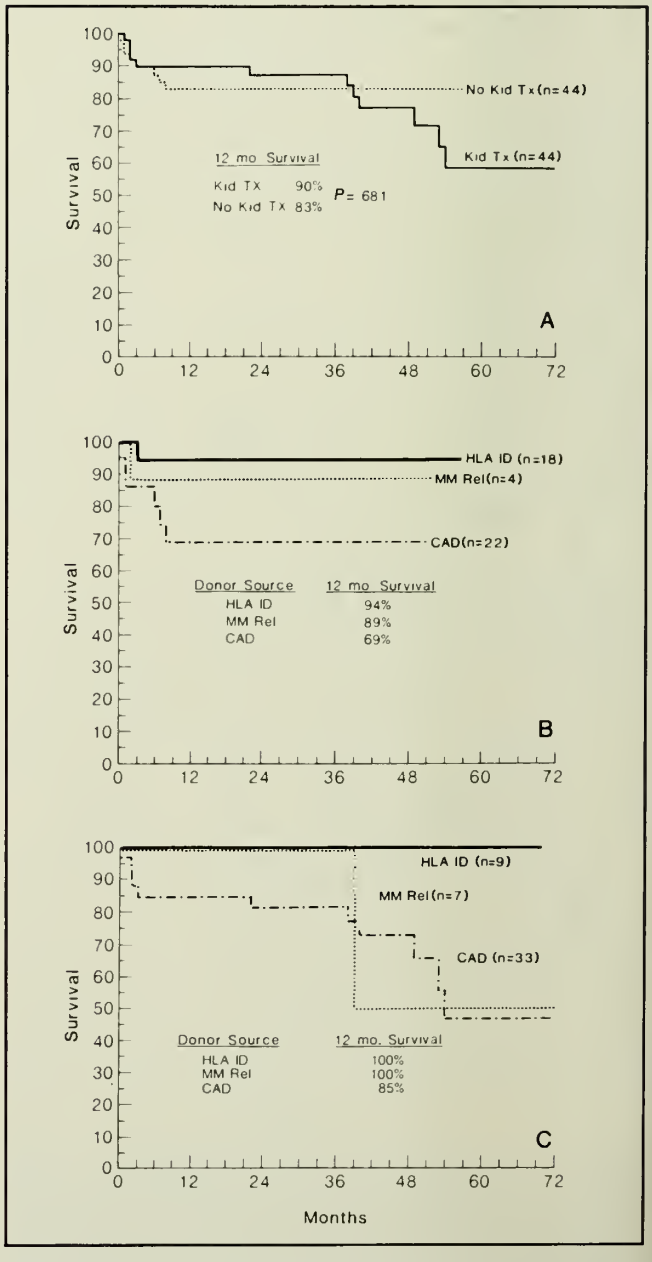

Figure 5.—Patient survival rates after pancreas transplantation, **A,** in those with (Kid TX) or without previous kidney grafts (No Kid TX), **B,** in those with previous kidney grafts according to pancreas donor source and **C,** in those without previous kidney grafts according to pancreas donor source. CAD = cadaver, HLA ID = human leukocyte antigen-identical, MM Rel = mismatched related

All patients have had detailed studies of eye, nerve and kidney function before and serially after pancreas transplantation.[15] Of the four patients whose pancreatic grafts functioned for more than four years, two had lesions noted by light microscopy that were typical of early diabetic nephropathy in kidney grafts transplanted nearly six years before the pancreas. In both patients, follow-up biopsy specimens appeared to show regression of the lesions. A possible influence of the pancreas transplant on diabetic retinopathy is difficult to ascertain in most patients, since either proliferative retinopathy was present—a stage where the eye disease is probably self-perpetuating independent of the degree of metabolic control—or the recipients had involutional retinopathy, which is also probably not influenced by metabolic control of diabetes. However, of three patients with preproliferative retinopathy who have been followed for more than a year, improvement occurred in two who were normotensive but not in one who had hypertension. Of four with proliferative retinopathy, three showed worsening (two had hypertension) and only one had improvement. Even though a beneficial effect of pancreas transplantation on retinopathy has not been shown, visual acuity improved in 8/16 patients (50%) with functioning grafts followed for more than a year and was stable in five patients (31%); only three had worsening (19%). In contrast, of 13 patients whose grafts failed early, 6 had worse vision at one year (46%) and none showed improvement. Neurologic studies at one year in patients whose grafts functioned did not show any significant changes in regard to quantitative measurements of autonomic function. An overall assessment, however, of neurologic status in 15 patients with functioning and 13 with failed grafts showed that 5 of the former were better (33%) while none of the latter were better, and only 1 with a functioning graft deteriorated (7%) compared with deterioration in 6 whose grafts failed early (46%).

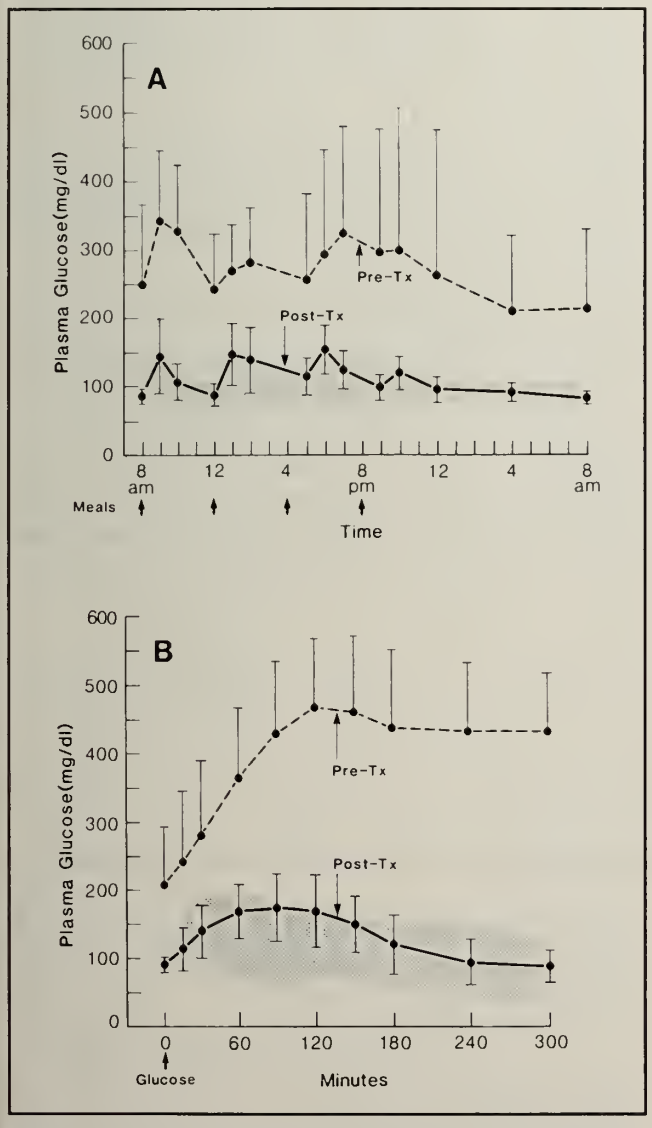

Figure 6.—Results (mean ± standard deviation [SD]) of metabolic studies in 18 patients with diabetes mellitus who have currently functioning pancreas grafts studied before (while on insulin therapy [Pre-Tx]) and at ≥1 year (12 to 80 months, mean 26 ± 21 months) after the transplant (no longer taking insulin; Post-Tx): **A,** 24-hour metabolic profile results and **B,** oral glucose tolerance test results. The shaded areas indicate the range (2 SD from mean) of values in 38 metabolic profiles and 42 oral glucose tolerance tests carried out in normal persons.

Discussion

Most pancreas transplants have been done in patients with diabetes who have far advanced complications, and most have had end-stage diabetic nephropathy treated with a kidney transplant either before or simultaneously with the pancreas transplant (see D. E. R. Sutherland and D. M. Kendall, "Pancreatic Islet Transplantation—Registry Report and Commentary," elsewhere in this issue). The benefit provided such patients by a pancreas transplant is uncertain, but because these patients already require immunosuppression to prevent rejection of the kidney, a pancreas transplant entails only the surgical risk and a case can be made for its application. A successful pancreas transplant may protect against the disease recurring in the transplanted kidney. However, it should be recognized that function deteriorates slowly and preexisting diabetic lesions in other systems are likely to take their toll before recurrent disease becomes a problem in the transplanted kidney.[16]

Although the present series began with application of a pancreas transplant to diabetic kidney-transplant recipients, we have changed our program so that most of the recipients now do not have uremia and have not had a kidney transplant. We attempt to identify persons who have diabetic complications that are not yet in the end stage but that, without intervention, will predictably be more serious than the possible side effects of a long-term immunosuppressive regimen. Most of our patients in recent years have been in this category (Figure 1). Although we initially thought that the use of cyclosporine would allow this group to be transplanted with a high success rate, we found that applying an immunosuppressive protocol (cyclosporine plus prednisone) that results in a high functional survival rate of renal allografts in recipients with uremia[17] did not prevent rejection of pancreas grafts. Twelve consecutive recipients of mismatched pancreas allografts who had had neither uremia nor a kidney transplant had graft rejection when immunosuppressed with a regimen of cyclosporine and prednisone alone. Persons who do not have uremia are more immunocompetent than those with uremia,[18] and we decided that the immunosuppressive regimens must be modified for transplantation in this group. For that reason, we began to use cyclosporine and azathioprine together because

experiments in animals had shown this combination to be very effective in preventing rejection of allografts.[19] The experience of other groups suggests that a cyclosporine and prednisone regimen is adequate for combined kidney and pancreas transplants in persons with uremia. However, in patients who do not have uremia, the use of cyclosporine and prednisone appears adequate only if the donor is an HLA-identical sibling, and even in this group rejections have occurred. For recipients of cadaver or mismatched related pancreas grafts (unless the relative was the donor of a previous kidney), the most effective protocol we have used has been a combination of cyclosporine, azathioprine and prednisone, with a 73% one-year actuarial functional survival rate for technically successful grafts. This protocol is particularly useful in patients with moderately advanced diabetic nephropathy because the cyclosporine dose can be adjusted downward to avoid superimposing cyclosporine nephrotoxicity on a diseased kidney and the azathioprine dose can be adjusted upwards to prevent rejection. This protocol has also been effective in preventing rejection of kidney transplants, with minimal toxicity to the recipients.[20]

In summary, our current approach is to transplant pancreas grafts to patients who do not have uremia whose diabetic complications are in the premorbid stage, to drain the graft of exocrine secretions into a hollow viscus and to give cyclosporine-azathioprine-prednisone therapy for immunosuppression. This protocol has evolved as the most successful we have tried.

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Pancreas Transplantation—Registry Report and a Commentary

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From December 1966 through December 1984, there were 561 pancreas transplants reported to the American College of Surgeons/National Institutes of Health Organ Transplant Registry, including 60 from 1966 through June 1977, 206 from July 1977 through December 1982 and 295 from January 1983 through December 1984. One-year graft function-survival rates (insulin-independent) in each of the three periods were 3%, 20% and 40%, and the corresponding patient survival rates were 40%, 72% and 77%. Currently 140 patients have functioning grafts, 76 for more than one year. Of the transplants since July 1977, one-year graft survival rates according to technique are 41% for enteric drainage (N = 155), 30% for polymer injection (N = 260) and 29% for urinary drainage (N = 47). Pancreas graft survival rates at one year according to whether or not the recipients have had a kidney transplant were 35% for recipients of simultaneous grafts (N = 281), 28% in recipients of a pancreas after a kidney (N = 112) and 26% in recipients of a pancreas only who did not have uremia (N = 106); corresponding patient survival rates were 69%, 83% and 83%. Overall, one-year pancreas graft survival rates according to whether the patients did or did not have end-stage diabetic nephropathy were 33% versus 25% and the corresponding patient survival rates were 73% versus 84% ($P < .01$). Patient survival rates were significantly higher in those without than in those with end-stage diabetic nephropathy. An analysis of technically successful grafts according to principal immunosuppressant showed one-year function rates of 46% in 258 cyclosporine-treated recipients and 26% in 143 azathioprine-treated recipients.

Pancreas graft survival rates have progressively improved and the procedure has become safer with advances in surgical technique and immunosuppression. Pancreas transplantation is currently applicable to patients with diabetes mellitus whose complications are, or predictably will be, more serious than the possible side effects of long-term immunosuppression.

(Sutherland DER, Kendall DM: Pancreas transplantation—Registry report and a commentary, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:845-852)

Pancreas transplantation for the treatment of diabetes mellitus has increased dramatically in recent years.[1] More pancreas transplants (295) were done in the two years from January 1, 1983, to December 31, 1984, than during the preceding 17 years (266) following the first transplant carried out by Kelly, Lillehei and associates in 1966.[2]

Evidence that the complications of diabetes are due to disordered metabolism is very convincing.[3] Many diabetologists make intense efforts to maintain nearly constant euglycemia in patients with diabetes,[4] but the new techniques of exogenous insulin delivery currently being used have risks, specifically hypoglycemia.[5] The most physiologic approach to maintain euglycemia in the treatment of diabetes is pancreas transplantation. The procedure has had limited application because of immunologic and technical problems, but these problems are gradually being overcome, and the number of successful transplants has increased in recent years.

The American College of Surgeons/National Institutes of Health (ACS/NIH) Organ Transplant Registry received information on 57 pancreas transplants in 55 diabetic patients from December 17, 1966, to June 30, 1977, when the registry closed.[6] Three pancreas transplants, one primary and two secondary, done in 1976 were not reported to the ACS/NIH registry but to the new International Human Pancreas Transplant Registry.[7] The new registry has received information on all known cases of pancreas transplantation since July 1,

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1977.[1] The data on vascularized pancreas transplant cases reported to the registry from December 17, 1966, through December 31, 1984, are summarized herein, and the emerging role of pancreas transplantation in the treatment of diabetes is discussed.

Number and Overall Results of Pancreas Transplantation

Between December 17, 1966, and December 31, 1984, 561 pancreas transplants were carried out at 60 institutions in 525 patients with diabetes mellitus (Figure 1). Cadaver donors were the source of 460 transplants—424 primary, 33 secondary and 3 tertiary grafts—and living related donors were the source of 41 primary grafts. In all, 501 of the transplants (in 469 patients) were done since July 1, 1977. Two patients in the new registry had had previous pancreas transplants recorded by the ACS/NIH registry.

Between January 11, 1985, and May 1, 1985, 140 patients were listed in the registry as having functioning grafts (insulin-independent), 76 for more than one year. Most of the recipients with functioning grafts had normal blood glucose levels, but the results of metabolic studies can be variable.[8,9] All of the grafts that are currently functioning were transplanted since 1978. Information on the number and results of transplants at each institution and references to the work of the various institutions that have published on their experiences are given in a recent comprehensive review article.[10]

The actuarial graft function and patient survival rate curves for all pancreas transplant cases, calculated according to the period on May 1, 1985, are shown in Figure 2. The results have improved in recent years, and pancreas transplantation has become safer. For 56 recipients of 60 grafts transplanted before July 1, 1977, the one-year actuarial graft function-survival rate was 3% and the patient survival rate was only 40%. In contrast, of the 193 patients who received 206 transplants from July 1, 1977, to December 31, 1982, the one-year graft function-survival rate was 20% and the one-year patient survival rate was 72%. For cases done in 1983 and 1984 (295 transplants in 276 recipients), the one-year graft survival rate was 40% and the patient survival rate was 77%. In all, 106 patients have had grafts that functioned for at least one year, 2 in the old registry and 104 in the new registry.

Results of Pancreas Transplantation According to Association With or Without Kidney Grafts

Most pancreas transplant recipients have had diabetic nephropathy or other diabetic complications that were far advanced. Kidney transplants have been done in 377 (80%) of the 469 recipients of 501 pancreas grafts transplanted since July 1, 1977.

The pancreas transplant success rates have been approximately the same in patients who were not uremic and did not have a kidney transplant as in recipients of a kidney transplant (Figure 3-A). The functional survival rates of pancreas grafts transplanted either simultaneously with or after a kidney transplant have also been similar. Actuarial graft survival rates at one year were 35% in recipients of simultaneous kidney transplants, 29% in recipients of previous kidney transplants and 26% for those who had neither uremia nor a kidney transplant. The two recipients of kidney grafts after

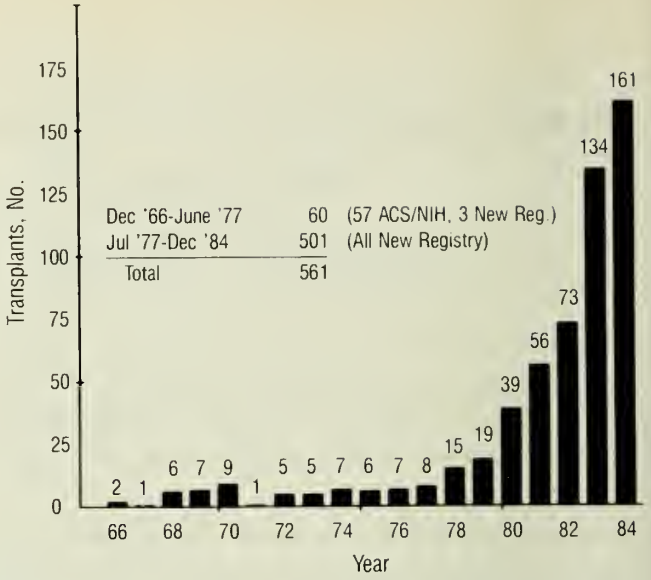

Figure 1.—Total number of pancreas transplants by year as reported to the American College of Surgeons/National Institutes of Health (ACS/NIH) Organ Transplant Registry and the International Pancreas Transplant Registry (New Reg.) between December 17, 1966, and December 31, 1984.

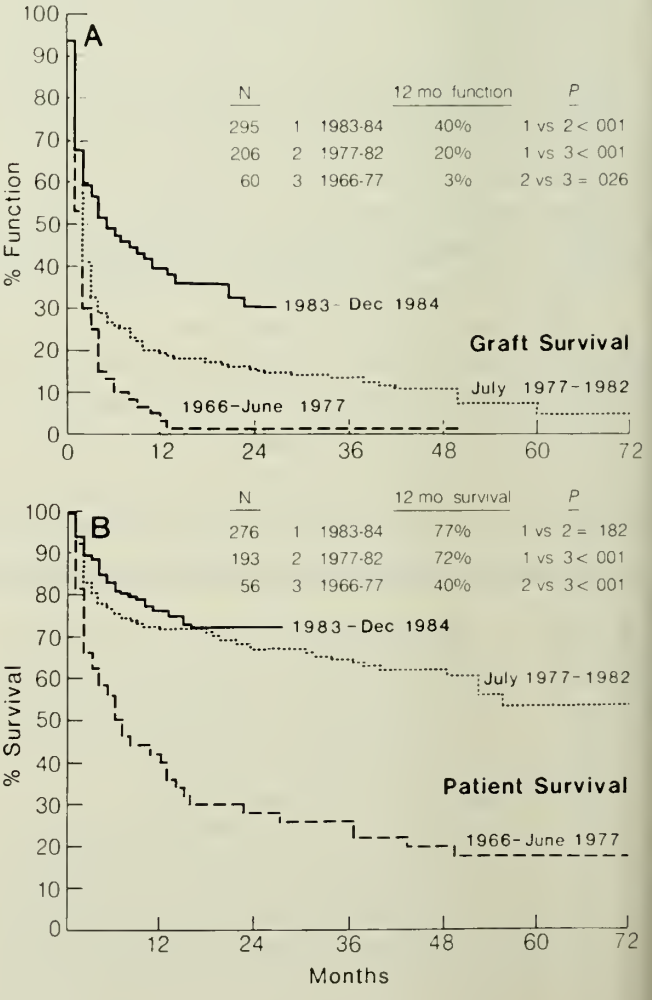

Figure 2.—**A,** Functional survival rates for all pancreas grafts, and **B,** patient survival for all primary pancreas transplant cases, reported to the registries (see text) by period of transplantation.

pancreas transplants lost pancreas graft function before their kidney transplants.

Patient survival rates have been higher in recipients of pancreas grafts only and in recipients of pancreas grafts after a successful kidney graft than in pancreas transplant recipients of simultaneous kidney grafts (Figure 3-B). Patient survival rates would be expected to be higher in recipients of pancreas transplants alone because the patients with diabetes who did not have uremia would be more likely to have less advanced complications than those with uremia. The fact that patient survival rates are also higher in patients with diabetic uremia who received a kidney transplant before a pancreas transplant than in those who received both grafts simultaneously, however, suggests that a penalty is paid for synchronous as opposed to asynchronous grafting in patients who have diabetic uremia. This interpretation is supported by an analysis of graft and patient survival rates according to whether the recipients of pancreas transplants did or did not have end-stage diabetic nephropathy. Pancreas graft survival rates were about the same in the two categories of recipients (Figure 4-A), but patient survival rates were significantly lower in patients who did than those who did not have end-stage diabetic nephropathy (Figure 4-B).

There is no evidence that pancreas transplants have improved the kidney transplant results in patients with diabetic uremia. Kidney graft function-survival rates, as well as patient survival rates, in pancreas transplant recipients with end-stage diabetic nephropathy are less than those reported for recipients of kidney transplants only who had diabetic uremia.[11,12] Thus it appears that correcting uremia by kidney transplantation is more important and more beneficial than total endocrine replacement therapy in patients with diabetes who have renal failure.

Results of Pancreas Transplantation According to Surgical Technique

Various surgical techniques have been used for pancreas transplantation, and grafts are classified according to whether they are a whole organ or a segment of the pancreas and according to the method used for duct management (occluded or drained into a hollow viscus). Duct occlusion is accomplished either by ligation or by injecting a synthetic polymer to obliterate the entire ductal system. Duct-drained grafts can be divided into those in which an anastomosis is made to either the gut or the urinary system (ureter or bladder).

The first pancreas transplant done was a segmental graft of only the distal portion of the gland.[2] In the ACS/NIH registry encompassing the period from 1966 to 1977,[6] however,

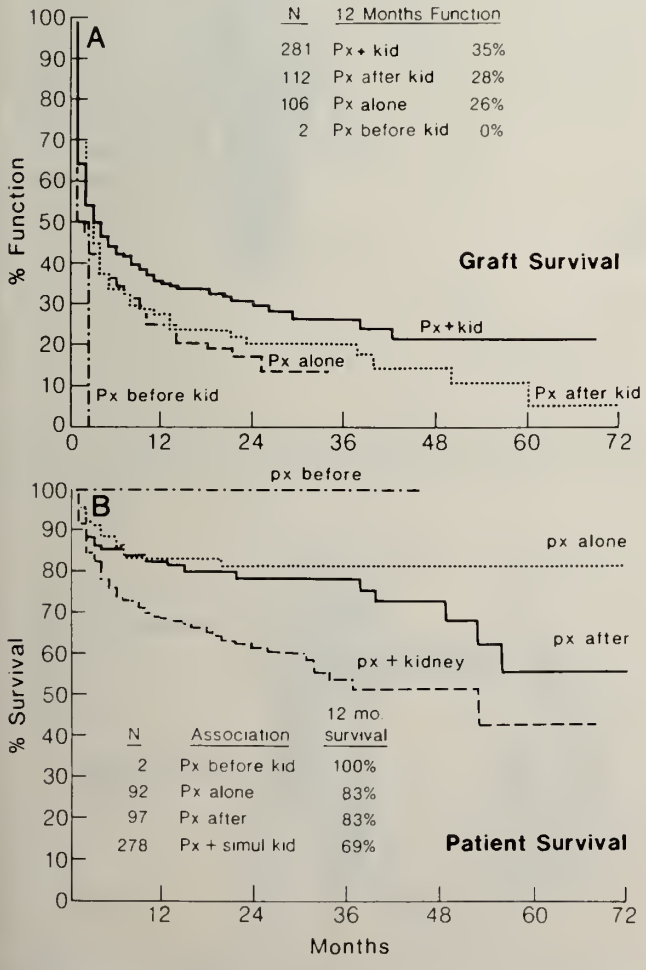

Figure 3.—A, Functional survival rates for all pancreas (Px) grafts, and **B,** patient survival rates for recipients of primary pancreas transplants done between July 1, 1977, and December 31, 1984, according to association with or without kidney transplants.

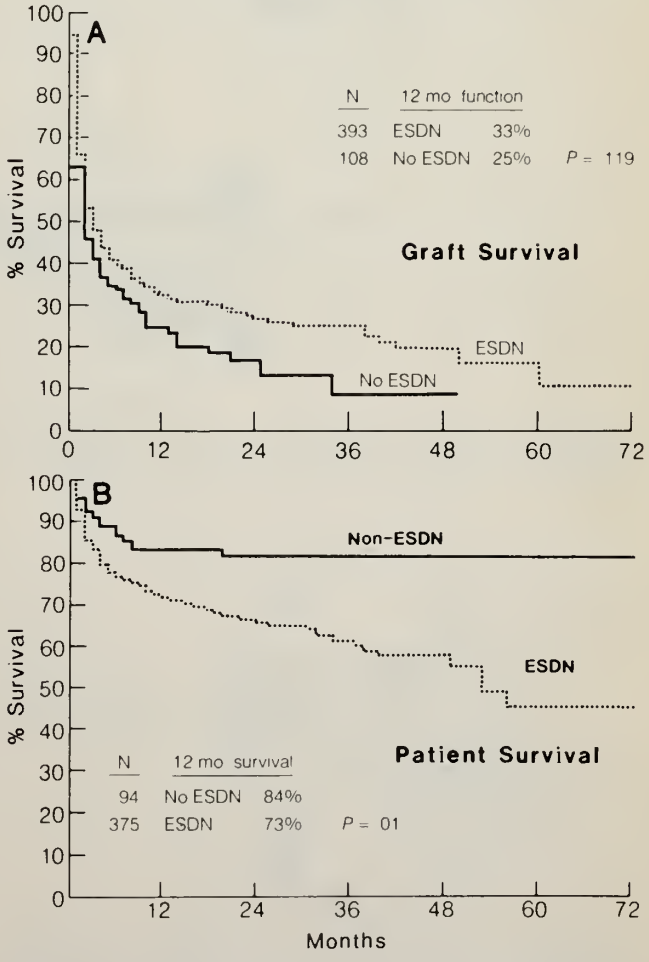

Figure 4.—A, Functional survival rates for all pancreas grafts, and **B,** patient survival rates for primary pancreas transplant cases done between July 1, 1977, and December 31, 1984, in recipients with or without end-stage diabetic nephropathy (ESDN).

nearly half of those transplanted were whole-organ pancreaticoduodenal grafts.[13] The high technical complication rate of pancreaticoduodenal transplants led to near abandonment of this approach by the mid-1970s and, until recently, the segmental technique was used almost exclusively (Figure 5). With this approach, the body and tail (approximately 50%) of the pancreas are removed and the donor celiac axis (or splenic artery) and portal vein (or splenic vein) are used for vascular anastomoses, usually to the iliac vessels of the recipient. The recipient's splenic vessels have also been used for anastomoses, resulting in drainage of the graft venous effluent into the portal circulation.[14,15] The techniques for removing segmental pancreas grafts from cadaver donors before[16,17] or after circulatory arrest[18] have been described.

The segmental approach allows living related donors to be the source of pancreas transplants (Figure 6).[19,20] The splenic artery and vein are ligated in the hilum of the spleen and the spleen survives on the collateral blood supply.[21] Metabolism remains normal if the donors have normal glucose tolerance before the hemipancreatectomy.[21,22] Of the 41 pancreas transplants from living related donors reported to the registry, 39 have been done at the University of Minnesota.[23]

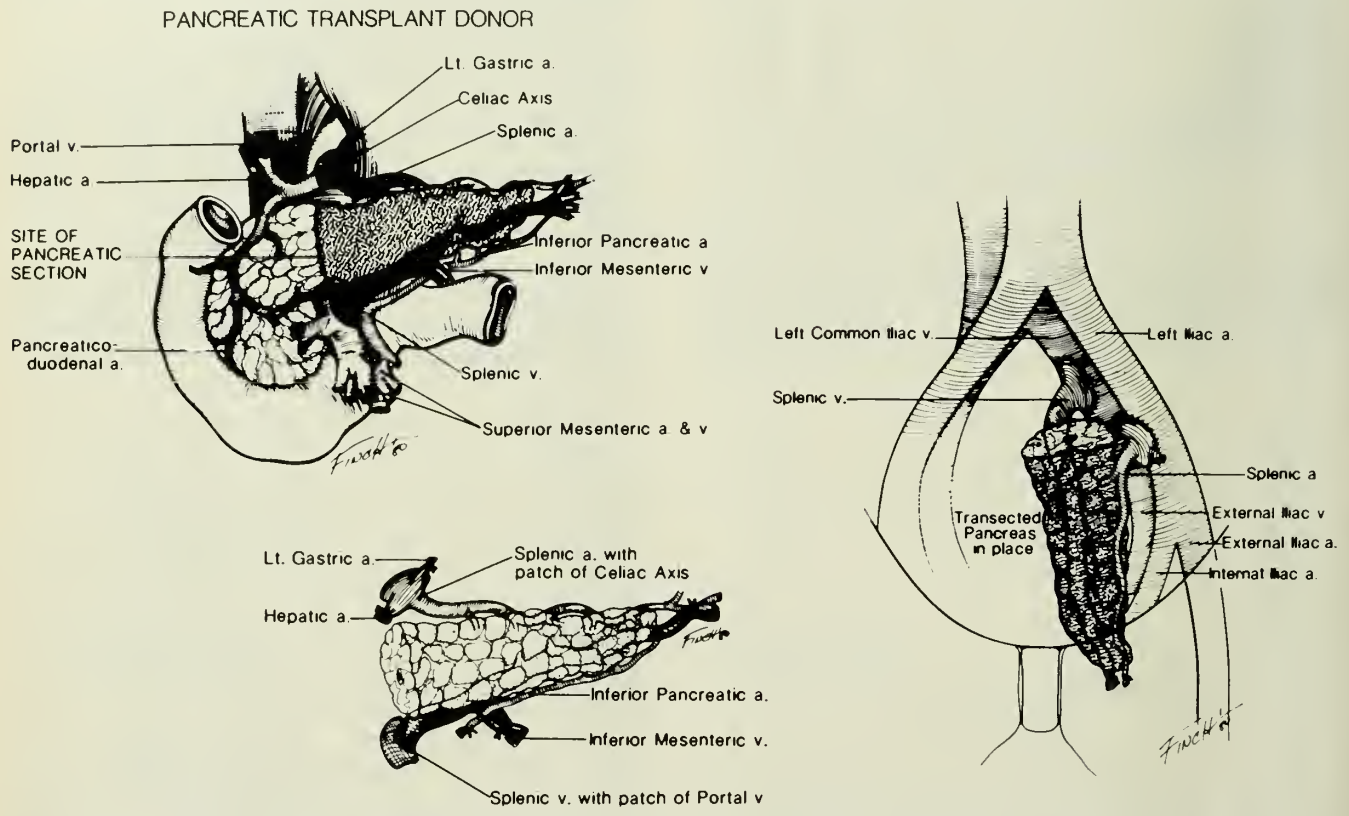

Figure 5.—Technique of segmental pancreas transplantation. Body and tail are transplanted with anastomoses of splenic vessels of donor pancreas to iliac vessels of recipient. (Reprinted with permission from Sutherland DER: Diabetologia 1981; 20:435, Springer-Verlag, New York, Publisher.)

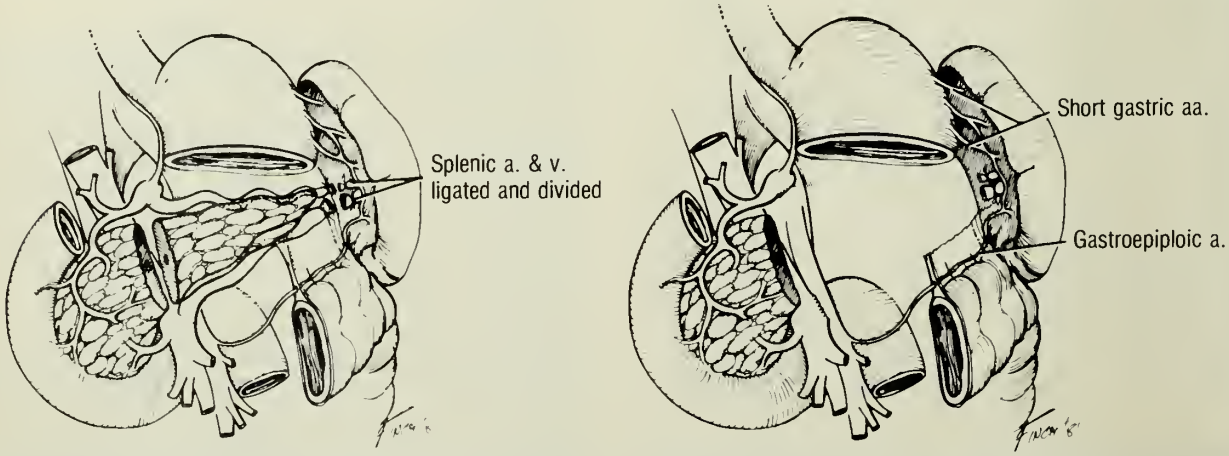

Figure 6.—Technique of distal pancreatectomy in living related donor for segmental transplantation. **Left,** Portion removed, showing ligation of distal splenic artery and vein. **Right,** Collateral blood supply to the donor spleen is preserved after excision of the pancreatic tail (from Sutherland et al[20]).

In recent years, there has been a renewed interest in transplantation of the entire pancreas from cadaver donors, with or without the duodenum. The entire duodenum can be transplanted, or the duodenum can be reduced to just a bubble encompassing the portion that is most intimate with the pancreas.[24] The pancreas also can be meticulously freed from the duodenum so that only the papilla of Vater is left attached, or it can be completely separated so that both the common bile duct and pancreatic duct are divided before they enter the duodenum.[25] The last approach obviates enteric contamination from the donor and has been used for duct management techniques that do not include drainage into a hollow viscus. Leaving a portion of the duodenum or the papilla has been used with the viscus drainage techniques. Some pancreas transplant surgeons have also left the spleen attached to the pancreas graft to increase the blood flow through the large splenic vessels,[24,26] but no advantage to this maneuver has been shown.[27]

The most important technical issue in pancreas transplantation is the provision made for managing the exocrine secretions. Several methods have been used. Suppressing exocrine function by polymer injection into the duct[17] has been the most widely used technique; 247 of 501 grafts transplanted since July 1, 1977, were duct-injected (49%). The complication rate for polymer injection remains relatively low, but fibrosis, induced by the injected agent, may involve the islets and lead to graft failure.[28] Duct ligation was used in the first pancreas transplant case[2] but has been used sporadically since July 1, 1977 (12 cases, 2%). The pancreatic duct can also be left open to drain freely into the peritoneal cavity,[29] and the secretions are absorbed if the pancreatic enzymes are not activated (22 cases since July 1, 1977, 4%). Pancreaticoenterostomy[30] and pancreaticoductoureterostomy[16] were used in some of the earliest pancreas transplant cases and have regained popularity. A variety of anastomotic techniques have been used, including direct insertion of the pancreatic duct into the bladder.[31] Enteric drainage has been established most often by an intussusceptive technique for segmental grafts (Figure 7) and by mucosa-to-mucosa anastomosis for whole pancreas[32] or pancreaticoduodenal grafts.[22] Pancreaticoenterostomy[14,33-35] has been done in 157 cases and urinary drainage[15,31,36] in 47 cases (19 ureter, 28 bladder) since July 1, 1977 (31% and 9%, respectively).

Except for ligation, all methods of duct management have been associated with long-term graft function (Figure 8-A). The one-year actuarial function-survival rates of pancreas transplants since July 1, 1977, were 41% with enteric drainage, 30% with duct injection, 29% with urinary drainage and 14% for intraperitoneal open duct. The methods of duct management associated with the highest patient sur-

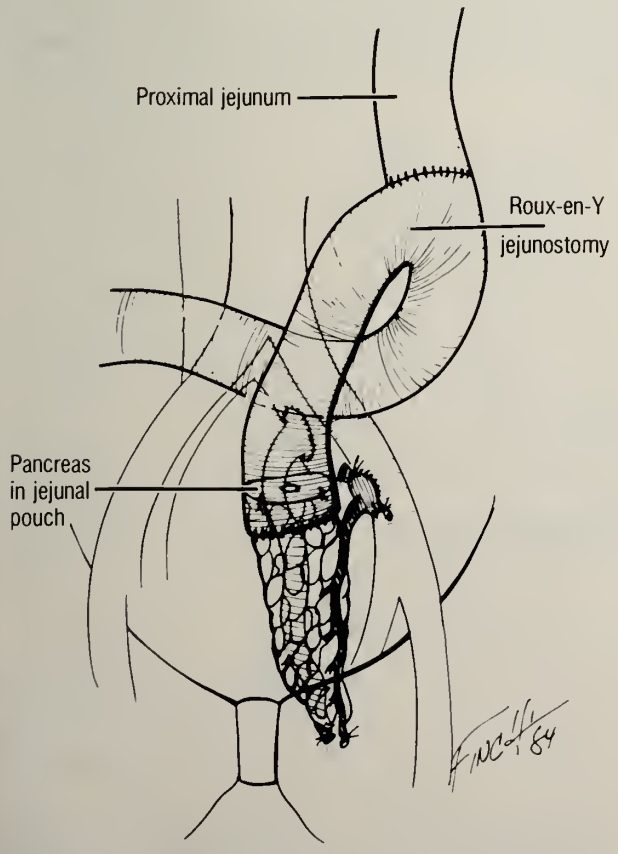

Figure 7.—Technique for drainage of the segmental pancreas graft exocrine secretion via a Roux-en-Y limb of recipient bowel (from Sutherland et al[20]).

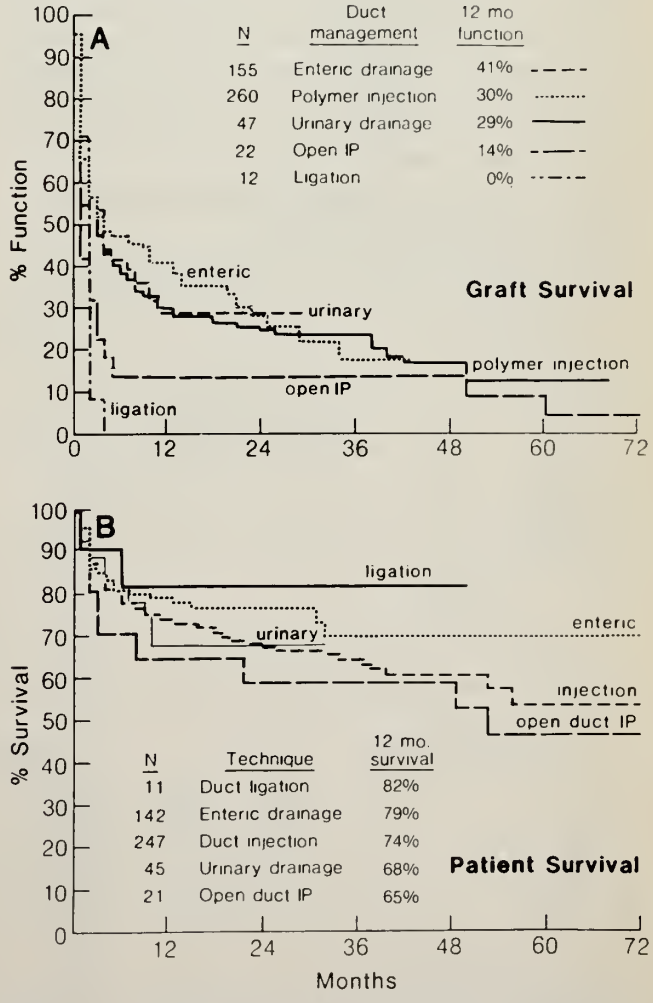

Figure 8.—**A**, Functional survival rates for all pancreas grafts, and **B**, patient survival rates for recipients of primary pancreas transplants reported to the registry (see text) from July 1, 1977, to December 31, 1984, according to duct management technique, excluding three cases unclassified due to immediate technical failure. IP = intraperitoneal

vival rates have been ligation and enteric drainage, but none of the differences are statistically significant (Figure 8-B).

Of the 501 transplants since July 1, 1977, 78 were whole-pancreas grafts (16%), while 376 were segmental (hemipancreas) grafts. The graft function-survival rates for both types were similar overall (Figure 9-A) and within the duct-injection (Figure 9-B) and enteric-drainage (Figure 9-C) categories. With urinary drainage, graft survival rates were higher for whole than for segmental grafts (Figure 9-D), but in this category the functional survival rate for whole-pancreas grafts was less than the survival rates of segmental grafts in the duct-injected and of both whole-pancreas and segmental grafts in the enteric-drainage categories.

Results of Pancreas Transplantation According to Immunosuppression in Recipients

Azathioprine was used to treat all those who received pancreas transplants before June 30, 1977. Since July 1, 1977, azathioprine has been the principal immunosuppressant in 182 recipients and cyclosporine in 310 recipients of pancreas allografts. An analysis according to immunosuppression showed that the pancreas allograft function-survival rates were significantly higher in all patients treated with cyclosporine than with azathioprine—37% versus 21% at one year (Figure 10-A). When technically successful transplants only were considered, the one-year pancreas allograft function rates in 257 cyclosporine- and 143 azathioprine-treated recipients were 46% and 26%, respectively (Figure 10-B).

Results of Pancreas Transplant According to Duration of Graft Preservation

Some of the pancreas grafts were transplanted immediately following removal from a donor. Of the cases since July 1, 1977, the interval between removal from a donor and transplantation to a recipient was reported on 382 grafts preserved by hypothermic storage in electrolyte solutions. The function-survival rate was higher for grafts preserved for less than six hours than for those stored more than six hours (Figure 11). A longer storage time was associated with a higher percentage of early (less than three days) graft failures, but late losses were nearly equivalent. At one year the graft survival rates were 34% for the less than six hours and 26% for the more than six hours preservation groups. An analysis done earlier had shown that the immediate function rates were similar for all storage times up to 24 hours.[37] The logistical aspects of pancreas transplantation[38] have been greatly facilitated by the capacity to preserve pancreas grafts.

Discussion

Nearly a third of the pancreas transplants worldwide since 1966 were done in 1984, emphasizing the fact that there has been a renewed interest in pancreas transplantation in recent years. The success rate is steadily improving (Figure 2). Long-term graft function with normal or near-normal glucose metabolism has been sustained in several patients.[8,9,23,39] Ultimately, pancreas transplantation should have the same impact on the treatment of diabetes as kidney transplantation has had on the treatment of end-stage renal disease. Observations in pancreas transplant recipients may also provide answers to many fundamental questions related to the nature of diabetes mellitus.[40]

Most pancreas graft recipients have had secondary complications of diabetes that were far advanced before transplantation. Ideally, pancreas transplantation should be done in the early stages of the disease. This approach is being taken,

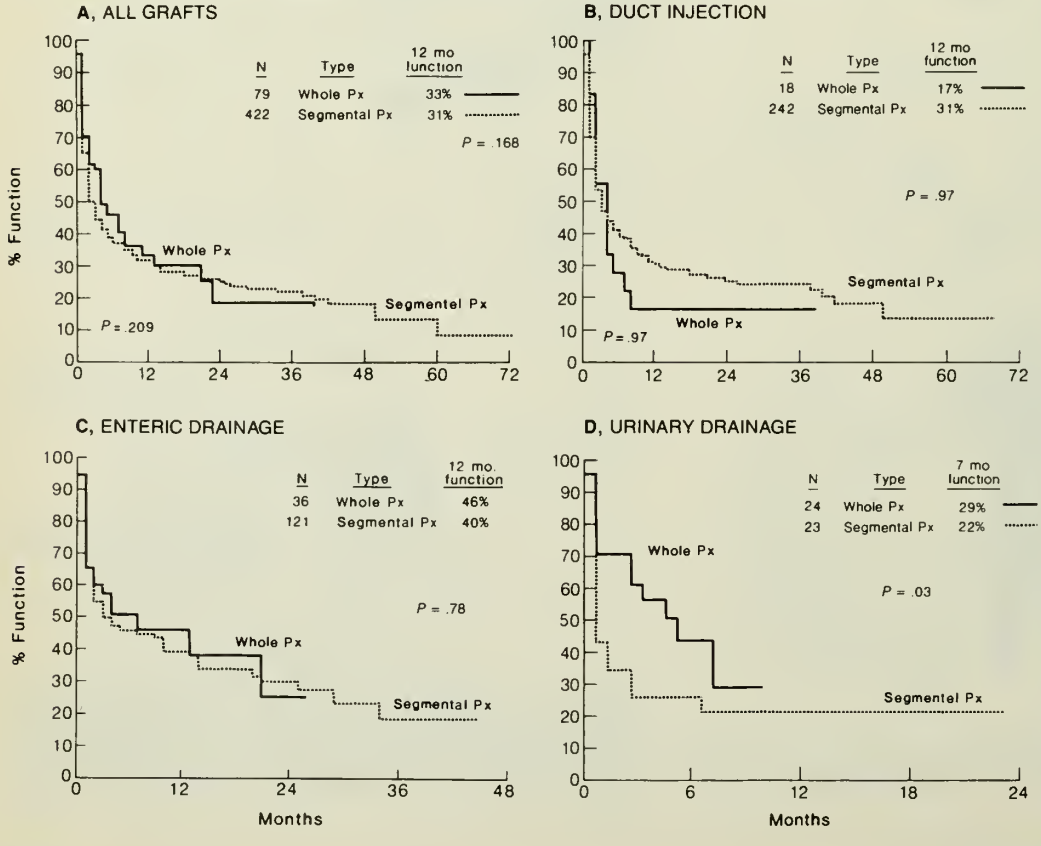

Figure 9.—Functional survival rate of whole pancreas (Px) versus segmental pancreas grafts reported to the registry (see text) from July 1, 1977, to December 31, 1984, for **A**, all cases and for those subjected to, **B**, duct-injection, **C**, enteric drainage or **D**, urinary drainage. Note differences in scale for **C** and **D**.

particularly in the recent Minnesota series.[22,23]* Because generalized immunosuppression is needed to prevent rejection, however, the diabetic patients selected must clearly be difficult to manage or be at high risk for secondary complications if subjected to conventional (exogenous insulin) treatment.

Immune rejection has been the greatest hindrance to successful pancreas transplantation. The use of cyclosporine has been associated with an improvement in the results of pancreas transplantation (Figure 10), and its use has expanded the population that can be considered for pancreas transplantation. The success rate of pancreas transplantation, however, is still less than that reported for kidney transplantation,[11] and modifications in immunosuppressive regimens are being explored in attempts to further improve pancreas graft function-survival rates.[23,26]

An alternative to pancreas transplantation is islet transplantation, but clinical attempts with islet allografts so far have been unsuccessful in making the recipients insulin-independent.[41-45] The manipulations that have led to a relatively high success rate in experiments with animals[46,47]† are difficult to apply to the human pancreas. Islet isolation and transplantation are complicated procedures for a transplant team, and it is very difficult to procure a sufficient quantity of viable islet tissue from a single donor pancreas. At this time it is uncertain whether the methods used in animals for processing islets and reducing their immunogenicity are practical for humans, and the future of clinical islet transplantation remains problematic.

In selected patients who have diabetes, pancreas transplantation currently can be carried out with a reasonable expectation of success. Because generalized immunosuppression is needed to prevent rejection, pancreas transplantation has been restricted to patients whose problems related to diabetes are, or predictably will be, more serious than the potential side effects of antirejection therapy. Patients who need or who have had a kidney transplant, and who require immunosuppressive therapy, meet these criteria. Some transplant patients, however, who have had neither uremia nor a kidney transplant are also in this category, such as those with preproliferative retinopathy and who are thus at great risk for a loss of vision,[48] or those with albuminuria who thus have early but progressive diabetic nephropathy.[49]

If immunosuppressive therapy improves to the point where the side effects are minimal, the limiting factor for the treatment of diabetes by transplantation will be the availability of donor pancreases. This problem is solvable. More than 6,000 kidney transplants are done in the United States each year.[50] The incidence of new cases of type I diabetes in the United States has been estimated to be 10,000 per year, and serious complications develop in less than half of the patients with the disease.[51]

The current kidney transplant rate, thus, is the same as the yearly incidence of complication-prone type I diabetes. Currently, only a small proportion of possible donors is used as a source of organs.[52] It should be possible to increase the procurement rate, and each donor could give a pancreas as well as kidneys and other organs for persons with and without diabetes who need transplants.

High plasma levels of insulinlike growth factors[53] and of inactive renin,[54] as well as the presence of joint stiffness,[55] have been reported to identify patients with diabetes who are

*See "One Institution's Experience with Pancreas Transplantation," by Sutherland and co-workers elsewhere in this issue.

†See "Pancreatic Islet Transplantation—Experimental and Clinical Potential" by Lafferty elsewhere in this issue.

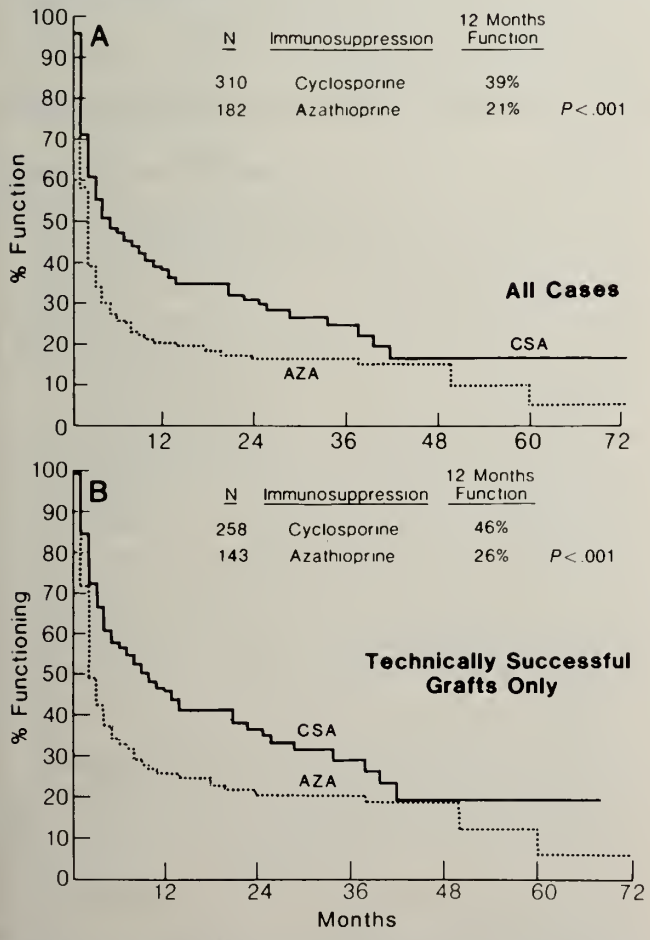

Figure 10.—Pancreas allograft survival rates for, **A**, all cases and, **B**, technically successful cases only reported to the registry between July 1, 1977, and December 31, 1984, according to principal immunosuppressant drug used in the recipients. AZA = azathioprine, CSA = cyclosporine (Cyclosporin A)

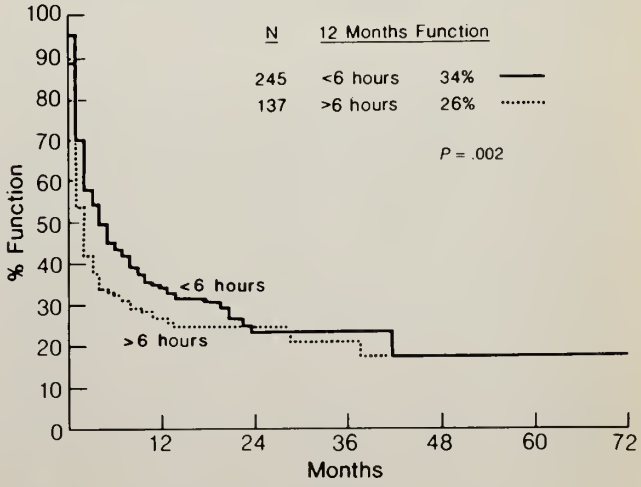

Figure 11.—Cadaver pancreas graft function-survival rates according to preservation times for cases reported to the registry with this information between July 1, 1977, and December 31, 1984.

at high risk for the development of secondary complications. Patients with diabetes who have impaired counterregulatory mechanisms and who are at high risk for hypoglycemic reactions while using an insulin pump or on other intensified insulin therapy regimens can be identified.[5] Persons with these characteristics will derive the most benefit from a successful pancreas transplant,[5,53-58] and a sufficient supply of pancreases from cadaver and related donors should be available for this select group. Preliminary observations in patients studied before and after pancreas transplantation suggest that the course of secondary complications of diabetes is favorably influenced by the presence of a functioning graft.[56,57]

In conclusion, pancreas transplantation has become increasingly effective for the treatment of human diabetes. Islet transplants have been successful only in the laboratory. Until the yield of viable human islets can be increased and their immunogenicity reduced, pancreas transplantation is the only practical method of total endocrine replacement therapy in diabetes. Pancreas transplantation potentially could be applied on as large a scale as renal transplantation. Eventually, pancreas transplantation may be routinely done at a stage early enough to prevent the development of diabetic nephropathy and other complications, and it would supercede kidney transplantation and other procedures in the management of a complication-prone patient with diabetes.

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Pancreatic Islet Transplantation—Experimental Experience and Clinical Potential

KEVIN J. LAFFERTY, PhD, *Denver*

New theoretic developments in transplantation biology indicate that it is possible to reduce the immunogenicity of a graft by removing antigen-presenting cells (leukocytes) from the tissue before grafting. Also becoming apparent is that cellular replacement therapy, the grafting of cells or clusters of cells, can be used to treat metabolic disorders such as type I diabetes mellitus. In the past, immune rejection has been a major problem and long-term patient immunosuppression is not warranted in patients with type I diabetes. Results of studies in animals show that under defined genetic conditions, mature islet tissue or immature fetal proislets may be transplanted across major histocompatibility barriers without a requirement for recipient immunosuppression. We are now ready to commence applying this technology clinically. These developments will initially be very experimental and limited in scope but should accelerate as data emerge from the initial trials.

(Lafferty KJ: Pancreatic islet transplantation—Experimental experience and clinical potential, *In* High-tech medicine [Special Issue]. West J Med 1985 Dec; 143:853-857)

Recently there have been two new developments in transplantation biology. The first is the return of the passenger leukocyte concept, although not in its original form that saw the mobile lymphoid cell as a vehicle for transporting transplantation antigen to a regional lymph node where it initiated an immune response, resulting in rejection of the grafted tissue. The new concept is somewhat more sophisticated. We now recognize that the transplantation antigen per se is not the major barrier to tissue grafting. This is because two signals, antigen and a source of costimulator activity, are required to trigger the antigen-specific lymphocyte response. Antigen-binding by the T-cell receptor provides one signal, and costimulator activity is the second signal. Interleukin 1 possesses costimulator activity, but may not be the only molecule that expresses such activity. Cells that provide a source of costimulator activity are said to express the S^+ phenotype, and such cells (stimulator cells) present alloantigen in a highly immunogeneic form to responsive T cells because they provide both signals required for T-cell activation. Stimulator cells are cells of lymphoreticular origin, possibly tissue dendritic cells; we cannot be sure that these are the only potential stimulator cells. The S^+ cells carried in a graft provide the major source of tissue immunogenicity, and it is for this reason that passenger leukocytes play such an important role in activating the allograft response.[1]

The second development is the use of cellular replacement therapy for the treatment of metabolic defects. An example of this approach is the use of either isolated islet cells, islets or proislets as a source of insulin-producing tissue that can be transplanted for the treatment of diabetes. This represents a shift away from the concept of organ transplantation as a treatment for this disorder, and provides an ideal model with which to test the concept that it is possible to reduce tissue immunogenicity by removing passenger leukocytes (S^+ cells) before transplantation.

In this article, I discuss experience with this approach in using islets, fetal pancreas and fetal proislet transplantation as a treatment for insulin-dependent diabetes mellitus in rodent systems and the potential for applying this technology clinically.

Syngeneic Islet Transplantation

The early work of Lacy's group in St Louis on isolating pancreatic islets and studying their physiology led to the notion that transplantation of this tissue could be used to correct the metabolic defect of insulin-dependent diabetes.[2] Initial studies using syngeneic transplantation involved implanting islet tissue into the liver, a site considered appropriate in view of the action of insulin in this organ. More recent studies have shown, however, that the tissue functions equally well when transplanted to the renal capsule of recipient animals.[3] It is likely that the good results seen in relation to kidney capsule transplantation merely reflect the appropriateness of this site for tissue transplantation. While it is probably beneficial to

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have the insulin delivered into the portal circulation, it would appear that implanting islets into the liver itself is not the most efficient form of transplantation. Transplanted islet tissue has also been shown to prevent development of the vascular complications of diabetes.[4]

The site of implantation is important when considering islet grafting as a treatment for diabetes. Islet tissue can be implanted at an intramuscular site where it becomes revascularized and granulated β-cells develop. This site is attractive in terms of access. However, both our group using transplanted fetal pancreas (unpublished results) and Lacy's group working with adult islets[2] found that tissue could be transplanted to an intramuscular site where granulated β cells developed, but in neither case would such transplants correct the metabolic defect. The same or even a smaller amount of tissue transplanted to the renal capsule did reverse the diabetes in these animals.[3,5] We have evaluated a number of different transplantation sites in pigs by comparing the survival of thyroid autografts transplanted subcutaneously, intramuscularly, beneath the renal capsule and in an omental pocket (C. J. Simeonovic, PhD; D. P. Dahll, MD, PhD; J. D. Wilson, MD, "A Comparative Study of Transplant Sites for Endocrine Tissue Transplantation in the Pancreas," submitted for publication). Best results were obtained with the renal capsule and the omental site. The omentum offers the advantage that its vascular bed drains into the portal circulation, and recently Yasunami and co-workers have shown that tissue transplanted in the omentum will reverse diabetes in rats.[6]

Allogeneic Islet Transplantation

From a physiologic standpoint, islet transplantation provides an attractive and effective approach to treating patients who have insulin-dependent diabetes. In the past, immune rejection has been a major problem and long-term patient immunosuppression is not warranted in the case of patients with diabetes. The demonstration, however, that the immunogenicity of tissues can be reduced by organ culture before transplantation has revolutionized our approach to this problem.[1] It allows allotransplantation of islet tissue without a need for immunosuppression of the recipient.

The organ culture technique was initially developed using thyroid and parathyroid transplantation.[7] Early attempts to apply this technique to the treatment of pancreatic islets before transplantation were frustrated by technical difficulties. The loss of tissue immunogenicity during culture is an oxygen-dependent phenomenon thought to result from the sensitivity of leukocytes to oxygen. Single pancreatic islets isolated from adult pancreata are extremely sensitive to oxygen and rapidly degenerate when cultured in an oxygen-rich atmosphere. This toxicity problem can be overcome by allowing groups of about 50 islets to aggregate and fuse together. Islet clusters are more resistant to oxygen toxicity and can be successfully allotransplanted in mice after one week of culture under these conditions.[8]

Following culture, islet allografts of seven islet clusters—that is, about 350 islets—have been shown to reverse streptozocin-induced diabetes in mice. Blood sugar levels of transplanted animals rapidly returned to normal, the animals became aglycosuric and they responded normally to the administration of glucose.[9] Uncultured islets, on the other hand, temporarily reverse diabetes, but the recipient animals return to a diabetic state within four weeks of transplantation.

TABLE 1.—*Transplantation of Cultured Islets Between Defined Mouse Strains and to Members of an Outbred (O/B) Mouse Colony*

Strain Combination	Donor Pretreatment	Number Transplanted	Survival N	Survival (%)
BALB/c+BALB/c	None	14	14	(100)
BALB/c+CBA .	None	20	20	(100)
BALB/c+O/B . .	None	22	5	(23)
BALB/c+O/B . .	Donors treated with cyclophosphamide (300 mg/kg) on days −4 and −2 and tissue harvested on day 0	16	9	(56)

More recently, we have also seen a synergism between cyclophosphamide pretreatment of a donor and organ culture of the islet tissue for one week in an oxygen-rich atmosphere. Cyclophosphamide treatment of donor animals before the harvest of tissue causes a profound decrease in the capacity of spleen cells to stimulate allogeneic T cells in culture.[7] This treatment has reduced the immunogenicity of thyroid allografts when administered four and two days before harvesting tissues for grafting. The drug is myelotoxic and has recently been shown to reduce the level of dendritic cells in tissues such as the kidney.[10] We have used this procedure to examine the feasibility of islet transplanting without immunosuppression to members of an outbred mouse population (Table 1). These studies were carried out by following the survival of cultured (BALB/c) islet clusters after transplanting to normal nonimmunosuppressed mice from either inbred colonies or from a colony of randomly bred mice (Table 1). Organ culture alone in an oxygen-rich atmosphere resulted in 100% allograft acceptance across the defined strain combination (BALB/c to CBA), but resulted in only 23% survival when the same tissue was transplanted in outbred animals. When organ culture was combined with cyclophosphamide pretreatment of the BALB/c donors, however, survival in the outbred population increased significantly to 56%. These results show the feasibility of allogeneic islet transplantation, without recipient immunosuppression, in an outbred animal population. They also emphasize the problems associated with genetic variability within the recipient populations. Such problems would have to be expected in a clinical situation.

Lacy's group achieved similar results in rats, but in their initial studies islets were not cultured in 95% oxygen, and allograft acceptance was only achieved when recipient animals were treated with a single dose of antilymphocytic serum at the time of transplantation.[11]

Tissue Immunogenicity

Progress has been made in understanding the mechanism whereby graft pretreatment before culture reduces tissue immunogenicity. Faustman and associates showed a dependence of islet immunogenicity on the presence of Ia-positive cells in transplanted tissue by achieving allograft survival following anti-Ia serum and complement treatment of the donor tissue before transplantation.[12] Ia antigen recognition is not an absolute requirement, however. Morrow and colleagues have shown that islet allograft rejection occurs when there is I-region compatibility between donor and recipient.[13] The fact

that rejection is dependent on the presence of an Ia-positive cell in the tissues is consistent with the notion that the stimulator cell (S^+) carries Ia antigen on its surface, but that recognizing Ia antigen is not a requirement for T-cell activation.

While the organ culture procedure reduces tissue immunogenicity, it does not alter antigen expression on the surface of a graft. The tissue is antigenic but weakly immunogenic. In the immediate posttransplant period, the tissue is in a metastable state, and the graft is acutely rejected when the recipient is challenged with living leukocytes of donor origin.[14] Procedures have now been developed that allow a graft to be stabilized following transplantation (see Development of Specific Tolerance below). The experimental investigation of cell populations to determine which cell types express the S^+ phenotype, as determined by their capacity to trigger graft rejection, have shown peritoneal cells to be active. B cells are inactive,[15] providing further evidence that expression of the Ia antigen is not a sufficient requirement for expression of the S^+ phenotype.[16] T cells can also trigger rejection, but only when they are used in a situation wherein the T cell can become activated in the host. This phenomenon probably reflects the fact that costimulator activity is a product of activated T cells. It is important to emphasize that more than one type of leukocyte can be involved in stimulating the specific allograft response.

Xenogeneic Islet Transplantation

Islet xenografts between discordant species (distantly related species) are rapidly rejected, often in a hyperacute manner. Xenografts of fish islets to rats, chick embryo islets to rats or mice and neonatal rabbit and calf islets to rats are all rejected within four days.[17] Xenografts between concordant (closely related) species have a rejection time similar to allografts. Transplants from rats to mice are rejected in two to five days.[17,18] If antilymphocyte serum is given at the time of transplantation, survival is prolonged to 10 to 12 days.[18] Islets used for these studies were obtained from crude pancreatic digests and were contaminated with nonislet tissue. A more carefully purified rat islet preparation survived for seven days in diabetic mice and up to eight weeks in immunosuppressed mice if large multiple doses of antilymphocyte serum were given.[19,20] Highly purified preparations of rat islets obtained by careful handpicking of pancreatic digests survived for 10 to 14 days in normal mice and from 15 to 82 days in mice that received one dose of antilymphocyte serum.[21] Cultivating such tissue in 95% oxygen extends the graft survival in normal mice to between 20 and more than 70 days.[22] Similarly, the survival of purified neonatal rat islets in mice was extensively prolonged, with rejection times of between 9 and 49 days.[23]

We have not been able to achieve long-term function of rat islet xenografts in diabetic mice (greater than 50 days) if the islets are taken from cyclophosphamide-pretreated donors and are cultured for 14 days in 95% oxygen before grafting to recipients that receive cyclosporine for the first 14 days posttransplantation (K. Lafferty, PhD, unpublished data, December 1983). Further studies are required to determine the minimal conditions needed to obtain such long-term xenograft survival. The fact that xenografts can be established in animals receiving minimal immunosuppression is encouraging, however.

Transplantation of Fetal Tissue

Pancreatic islet transplantation presents an attractive approach to treating patients with insulin-dependent diabetes, although attempts to isolate large numbers of islets from the human pancreas have been hindered by the very fibrous texture of adult tissue. Recent advances in the preparation of islets from large animals, however, forecast the potential feasibility of developing technical procedures for the large-scale isolation of human islets.[24] For practical reasons, fetal pancreas is the tissue of choice for clinical islet transplantation at the present time.

Isografts of a single fetal pancreas can reverse diabetes in rodents. The fetal pancreas is more immunogenic than adult islets, however. Allografts of fetal mouse pancreata that had been cultured for up to ten days before transplantation are acutely rejected when transplanted from BALB/c to CBA mice.[25] The rejection process is well established within two weeks of transplantation and, by four weeks, only scar tissue and scattered mononuclear cells remain at the graft site. This difference in behavior between adult islets and fetal pancreas is attributed to a large lymphoid component associated with the latter. This lymphoid tissue is not actually in the pancreas itself, but appears to represent developing lymph nodes associated with the mesentery that surrounds the rather diffuse rodent pancreas in situ. Large numbers of Ia-positive (dendritic?) cells have also been observed throughout fetal human pancreas.[26] We have observed lymphoid remnants in association with the ten-day cultured fetal pancreas, however, and it is likely that this residual lymphoid tissue triggers the rejection process. It is possible to successfully transplant fetal pancreata to nonimmunosuppressed allogeneic recipients following a longer (17- to 20-day) period of organ culture. However, the functional capacity of this tissue decreases as the culture period is increased.[5]

Fetal proislets, obtained by collagenase digestion and further culture of the fetal pancreas digest, provide a more promising tissue for the purpose of clinical transplantation in treating diabetes. Fetal mouse proislets are not highly immunogenic and can be successfully allotransplanted across a major histocompatibility barrier. At four weeks posttransplantation, about 50% of the proislet allografts contain differentiated islet tissue without any evidence of mononuclear cell infiltration. Remaining grafts were rejected.[27]

Fetal proislets develop into mature islets following transplantation. Histologic examination of freshly digested fetal pancreas shows the presence of differentiated acinar tissue, considerably disrupted after the collagenase treatment, and a small amount of undifferentiated tissue. After another four days in culture (atmosphere 10% of carbon dioxide in air), the digest units consist of discrete ovoid cellular aggregates containing undifferentiated cells, some tubular components, connective tissue and occasional peripheral regions of cellular organization that resemble endocrine tissue.[28] At this stage, the tissue shows only occasional insulin- and glucagon-containing cells when stained with immunoperoxidase-labeled antibody. After isotransplantation, however, the proislets developed into islets with normal morphology that stained for both insulin and glucagon; small numbers of dendritelike somatostatin-containing cells have also been observed in islets formed following proislet transplantation (K. Lafferty, PhD, unpublished data, November 1984).

TABLE 2.—*Reversal of Diabetes (Streptozocin-Induced) in CBA Mice Transplanted With Proislets Obtained From Varying Numbers of Fetal CBA Donors (17 Days' Gestation).*

Pancreas Equivalents Transplanted	Proportion Normoglycemic	Recovery Time (d)
8	6/7	20 - 93
6	6/6	12 - 76
4	8/8	8 - 62
2	4/7*	14 - 62

*Animals in this group have so far been observed for a maximum of 62 days.

Fetal proislets will function to reverse streptozocin-induced diabetes. Table 2 shows the results obtained when tissue from eight-, six-, four- and two-CBA fetal mouse donors was transplanted to the renal capsule of syngeneic recipients. Tissue from two fetal donors has the capacity to reverse diabetes, and animals that have reversed or become normoglycemic show a normal response to the oral administration of glucose.[9] The remaining three animals in this group, which have not reversed by 62 days, are still under investigation. We have preliminary evidence that tissue from one fetal donor will eventually render diabetic animals normoglycemic. It can take from four to six months, however, for this tissue to effectively control the diabetic condition. Human fetal proislets have been prepared by collagenase digestion of tissue obtained from aborted fetuses (12 to 16 weeks' gestation). Granulated β-cells develop when this tissue is transplanted to the kidney capsule of athymic mice. The development of this tissue is slow, and well-granulated β-cells are not usually seen until ten weeks or more after transplantation (K. Lafferty, PhD, unpublished data, November 1982). Fetal proislets appear, therefore, to be the most appropriate tissue for use in clinical islet transplantation.

Development of Specific Tolerance

Cultured allografts of both thyroid and pancreatic islet tissue carry recognizable antigen and can be promptly rejected when recipient animals are challenged with leukocytes of donor origin at the time of transplantation. However, animals carrying allografts for a prolonged period (equal to or greater than 100 days) become progressively more resistant to challenge with donor cells.[29] In the case of thyroid, we have found that grafted tissue retains antigen and that this adaptation of the graft to its host results from the development of tolerance in an adult recipient.[30] We argued that this phenomenon might develop as a result of slow leakage of free antigen into the immune system of the recipient, possibly inducing tolerance in a manner akin to active enhancement. Support for this notion has come from the pancreatic islet system. When transplanted animals are injected with ultraviolet-wave-killed donor spleen cells—a source of alloantigen on nonstimulating cells—around 30 days posttransplantation, graft rejection is not stimulated. Viable donor cells administered at this time promptly activate a rejection reaction. That is, the ultraviolet-irradiated cells were subsequently challenged with viable donor spleen cells and the allografts were not rejected. The ultraviolet-irradiated cells, which provide a source of antigen alone, have stimulated the development of tolerance in grafted animals. The specificity of this tolerance was shown by the fact that animals would accept an uncultured thyroid allograft of donor origin but would reject a third-party thyroid grafted to the same recipient at the same time. We have also shown, in the case of both thyroid- and islet-transplanted animals, that this phenomenon is not a deletion form of tolerance. Lymphocytes from "tolerant" animals respond normally to donor alloantigen in vitro.[14] Faustman and co-workers suggested that such unresponsiveness may result from the action of suppressor cells.[31]

In a recent publication, Lau and associates showed that pretreating rats with ultraviolet-irradiated blood from the putative donor strain would induce a stage of specific tolerance and allow prolonged acceptance and function of an untreated islet allograft. This tissue tolerance was also specific; animals transplanted with islets from a third-party donor rejected such grafts acutely, as did animals transplanted with islets in the absence of recipient pretreatment.[32]

The independent confimation by a number of laboratories that tissue tolerance can be induced in adult animals is one of the most exciting recent developments in transplantation biology. Our own experience in this area indicates that there may be a very delicate balance between inducing either tolerance or immunity following treatment of animals with ultraviolet-irradiated cells. Much work must be done to analyze the cellular and molecular basis of this phenomenon, and it would be premature to see it as the answer to the problems associated with the use of immunosuppression in clinical transplantation. It is unquestionably a fruitful area for further research, however.

Clinical Potential

As yet, there is only one published report of this approach to the treatment of diabetes in humans.[33] This report comes from Farkas and Karacsonyi working in Hungary who reported the results of infusing cultured human fetal proislet tissue into the liver of recipients with diabetes via the umbilical vein.[33] Both patients, who had severe retinopathy, were infused with tissue derived from two fetal donors that is ABO compatible with the recipient. Both recipients were immunosuppressed with steroids and azathioprine for seven to eight months following transplantation.

In both cases there was a significant drop in the daily insulin requirement, although neither patient became independent of insulin. Basal serum C-peptide levels were initially undetectable in one case and low (0.6 ng per ml) in the other. By eight to ten months posttransplantation, both patients had significant C-peptide levels (1.9 and 1.2 ng per ml, respectively), and at ten months following transplantation both patients showed a strong C-peptide response to oral glucose challenge. Progression of retinopathy was arrested in both cases.

This first report is encouraging. This new technology has begun to be applied to the clinical situation and it is hoped that this is the first step towards the development of cellular replacement therapy for the treatment of type I diabetes.

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January 24-25—**Private Sorrows, Public Issues: Brain Damage in Adults.** Family Survival Project at Cathedral Hill Hotel. Friday-Saturday. Contact: Family Survival Project, 921-5400.

January 25-26—**Psychodynamic Group Therapy—1986.** UCLA at Sheraton Grande, Los Angeles. Saturday-Sunday. 13 hrs. Fee: $250.

January 26-31—**12th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe. Sunday-Friday.

February 6-9—**Intensive Review of Psychiatry and Neurology.** UCLA at Hotel Del Coronado. Thursday-Sunday. 24 hrs.

RADIOLOGY

January 13-17—**Interventional MRI and Neuroradiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. Fee: $395.

January 31-February 2—**The 38th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 19 hrs. Contact: Diane L. Johnson, (213) 642-0921.

February 2-7—**7th Annual Winter Conference in the High Sierra.** American College of Medical Imaging at Caesars Tahoe Hotel. Sunday-Friday. 25 hrs. Contact: American College of Medical Imaging, (213) 275-1393.

February 3-7—**Radiology Imaging and Intervention.** UCSD at Hotel Intercontinental, San Diego. Monday-Friday. 23 hrs.

February 3-9—**The 12th Annual Post Conference Seminar.** Los Angeles Radiological Society at Wailea Beach Hotel, Maui. Monday-Sunday. 18 hrs. Contact: Diane Johnson, (213) 642-0921.

February 15-20—**Thoracic Imaging—1986.** Society of Thoracic Radiology at Newporter Beach Resort Hotel, Newport Beach. Saturday-Thursday. Contact: Ryals and Associates, (214) 659-9590.

March 3-4—**Neuroradiology Update.** UCSD at Hotel Del Coronado, San Diego. Monday-Tuesday. 11 hrs.

March 3-7—**Magnetic Resonance Imaging Update.** UCSD at Hotel Del Coronado, San Diego. Monday-Friday. 20 hrs.

March 10-14—**Diagnostic Imaging 1986: CT, Ultrasound MRI and Intervention Radiology.** UCSF at Waiohai Hotel, Hawaii. Monday-Friday. 24 hrs. Fee: $495.

March 24-28—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. Fee: $495.

April 28-May 2—**Annual San Diego Residents Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Monday-Friday. 35 hrs. Fee: $375.

SPORTS MEDICINE

January 19-24—**Sports Medicine: 1986 (A Primary Care Perspective).** UCD at Hyatt Lake Tahoe. Sunday-Friday.

March 17-21—**University of Hawaii Sports Medicine Course.** American Academy of Family Physicians at Pacific Beach Hotel, Honolulu. Monday-Friday. 18 hrs. Contact: Ms Joy Lewis, (808) 948-8244.

SURGERY

January 17-18—**8th Annual Surgical Postgraduate Course Catastrophic and Critical Surgical Problems.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday.

January 20-24—**9th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hotel Intercontinental, San Diego. Monday-Friday. 32 hrs.

March 13-15—**Moving Ahead: Amputation Rehabilitation A Multidisciplinary Approach.** Sharp Memorial Hospital at Holiday Inn, San Diego. Thursday-Saturday. 19 hrs. Fee: $225. Contact: Mary Dokmanovich, (619) 292-2551.

April 17-19—**Postgraduate Course in General Surgery.** UCSF at Hilton, San Francisco. Thursday-Saturday.

June 5-6—**The 15th Annual Neurosurgery Postgraduate Course and the 9th Annual Neurosurgical Nurses Conference.** UCSF at Meridien Hotel, San Francisco. Thursday-Friday.

OF INTEREST TO ALL PHYSICIANS

January 11—**New Applications of Calcium Channel Blockers.** UCSF at The St. Francis Hotel, San Francisco. Saturday. Fee: $25.

January 20-24—**Intensive Course in Geriatric Medicine.** UCLA at Miramar Sheraton, Santa Monica. Monday-Friday. 33 hrs.

January 29-31—**9th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn, San Diego. Wednesday-Friday. 21 hrs.

January 30-February 2—**Surgery for the Aging Face: Focusing on the Issues.** UCSD at Hotel Intercontinental, San Diego. Thursday-Sunday. 19 hrs.

(Continued on Page 872)

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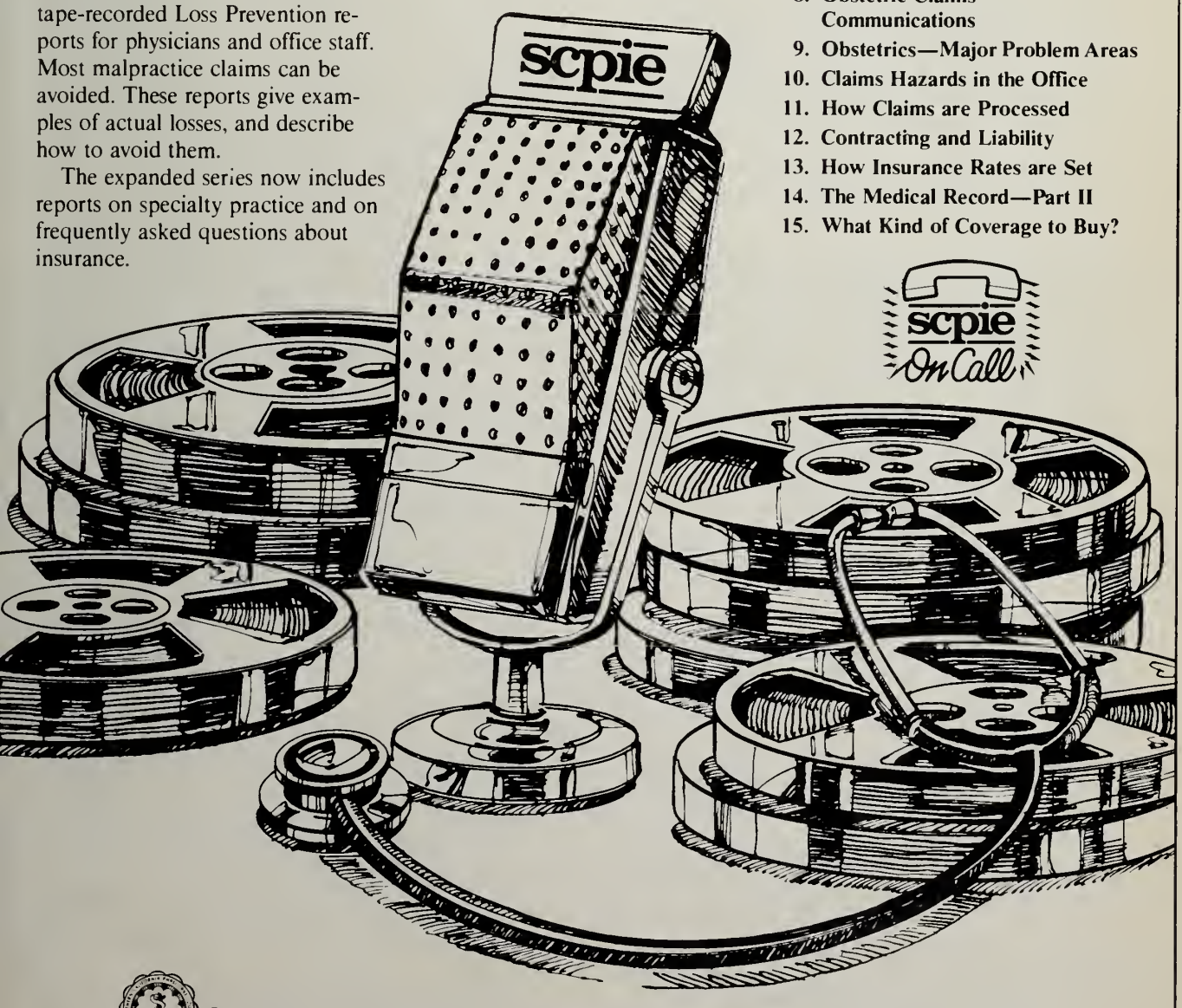

Sponsored by SOCAP: The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County and Ventura County.

(Continued from Page 870)

February 3-6—**Trauma Management 1986.** UCSD at U. S. Grant Hotel, San Diego. Monday-Thursday. 18 hrs.

February 5-7—**Clinical Laboratory Molecular Analyses: Emerging Technology and Future Trends.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Wednesday-Friday. 22 hrs. Contact: Scripps Clinic and Research, (619) 457-8556.

February 10-15—**The UCI Family Practice Refresher Course.** UCI at Hotel Meridien, Newport Beach. Monday-Saturday. 62 hrs.

February 19-21—**EMS Today-Administrative Instructor and Clinical Tracks.** UCSD at Holiday Inn, San Diego. Wednesday-Friday. 15 hrs. Fee: $240.

February 20-22—**Recent Advances in Reproductive Medicine.** Memorial Medical Center of Long Beach at Newport Beach Marriott Hotel. Thursday-Saturday. 14 hrs. Contact: Assistant Director Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach, CA 90801.

February 22-March 1—**Orthopedic Emergencies.** UCSD at Royal Lahaina Resort, Maui. One week. 21 hrs. Fee: $350.

February 27-March 2—**24th Annual Symposium on Critical Care Medicine.** UCLA at MGM Grand Hotel, Las Vegas. Thursday-Sunday.

February 28-March 5—**CMA Annual Session.** Bonaventure Hotel, Los Angeles. Friday-Wednesday.

March 1-2—**Annual Workshop San Francisco Academy of Hypnosis.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Saturday-Sunday. Fee: $300. Contact: Jan Brooks, (415) 826-0533.

March 8-15—**Pain Mechanisms and Management.** UCSF at Maui Inter-continental, Wailea. One week. 23 hrs. Fee: $350.

March 12-14—**36th Annual Course for Physicians in Family Practice.** Mount Zion Medical Center. San Francisco. Wednesday-Friday. Contact: Robin B. Jackson, (415) 885-7269.

March 14-16—**Office Emergencies in Primary Care.** UCSD at Hotel Del Coronado. Friday-Sunday. 18 hrs. Fee: $275.

March 21—**Nora Eccles Harrison Diabetes and Nutrition Update: Nutrition Controversies.** UCD at San Francisco Hilton. Friday. 5 hrs.

March 24-29—**Counseling Strategies for Physicians.** University of Texas at Oahu, Hawaii. Monday-Saturday. 17 hrs. Fee: $325. Contact: Sam A. Nioxon, 1 (800) 332-8747.

April 10-13—**67th Annual Session.** American College of Physicians at Moscone Center, San Francisco. Thursday-Sunday. Contact: Carol Trotman, (215) 243-1200.

April 30-May 4—**Eighth Annual Wound Management Workshop.** UCSD at Hyatt Islandia Hotel, San Diego. Wednesday-Sunday. 19 hrs.

IDAHO

February 1-8—**Sports Medicine.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 8-15—**Orthopaedics/Radiology.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 15-22—**Endocrinology/Diabetes.** University of Washington at Elkhorn Resort, Sun Valley. One week. Contact: U/W, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

MONTANA

See Montana listings under WASHINGTON.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

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CONTINUING MEDICAL EDUCATION

January 17-18—**Carrie Tingley Hospital Sixteenth Winter Orthopaedic Seminar.** Friday-Saturday. Albuquerque Hilton Inn. Contact: Office of Medical Affairs, Post Office Box 25447, Albuquerque, NM 87125. (505) 841-5000.

January 24-25—**Infectious Disease: Respiratory, Thyroid and Musculo-Skeletal Disorders.** Friday-Saturday. Albuquerque Marriott Hotel. 11 hrs. AMA Cat. I. Contact: Lovelace Medical Center, Office of CME, 5400 Gibson Blvd SE, Albuquerque, NM 87108. (505) 262-7353.

January 25-26—**New Mexico Chapter, American Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 13 hrs. AAFP Prescribed, New Mexico Required Education, Cat. I. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

January 31-February 3—**Murphy's Law in Orthopaedics.** Friday-Monday. Quail Ridge Inn (formerly Tennis Ranch of Taos). 16 hrs. AMA Cat. I and New Mexico Required Education, Cat. I. Contact: Barry Maron, MD, 8324 Constitution Pl. NE, Albuquerque 87110. (505) 292-6062.

February 10-14—**Taos Medical Symposium.** Monday-Friday. Quail Ridge Inn (formerly Tennis Ranch of Taos). 18 hrs, AMA Cat. I, NM Required Education, Cat. I. AAFP Prescribed credit. Contact: Dale A. Gray, MD, 3901 Georgia NE, Albuquerque 87110. (505) 881-6699.

February 14-16—**Second Annual Presbyterian Heart Institute Symposium—Case Studies in Cardiology.** Friday-Sunday. Presbyterian Hospital, Albuquerque. 19 hrs. AMA Cat. I, New Mexico Required Education, Cat. I. Contact: Gilbert Raff, MD, 201 Cedar SE, #604, Albuquerque 87106. (505) 242-2796.

February 20-22—**19th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. Hilton Inn. AMA Cat. I. Contact: UNM.

February 27-March 1—**Second Annual Ruidoso Heart Symposium—Practical Cardiology Update.** Thursday-Saturday. Inn of the Mountain Gods. 16 hrs. AMA Cat. I, NM Required Educa-

CONTACT INFORMATION

UNM—Contact: University of New Mexico School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

tion, Cat. I. Contact: American Heart Association, NM Affiliate, (505) 268-3711.

February 27-March 1—**Santa Fe Conference on Humans as Research Subjects: Issues and Concerns to Institutional Boards and Clinical Investigators.** Thursday-Saturday. Inn at Loretto. Contact: Lovelace Medical Center, Office of CME, 5400 Gibson Blvd SE, Albuquerque, NM 87108. (505) 262-7353.

March 5-8—**Durango Sports Medicine Conference.** Wednesday-Saturday. Contact: Lovelace Medical Center, Office of CME, 5400 Gibson Blvd SE, Albuquerque, NM 87108. (505) 262-7353.

March 8—**New Mexico Pediatric Society—Wylder Lecture—Pediatric Allergies.** Saturday. School of Nursing Building, UNM Campus. 4.5 hrs. AMA Cat. I, NM Required Education, Cat. I. Contact: Marilyn Stark, NM Pediatric Association, 7605 Mountain Rd NE, Albuquerque 87110. (505) 265-7431.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

(Continued on Page 876)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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(Continued from Page 874)

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

FAMILY PRACTICE

February 10-14—**Family Practice Review.** Portland. Monday-Friday. Red Lion/Lloyd Center. Contact: OHSU-CME.

March 28—**Geriatrics.** Portland. Red Lion/Lloyd Center. Friday. Contact: OHSU-CME.

NEPHROLOGY

January 11—**Continuous Arteriovenous Hemofiltration.** Oregon Health Sciences University-UHS 8B-60. Saturday. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

January 17—**Infectious Diseases.** Portland. Oregon Health Sciences University Library Auditorium. Friday. Contact: OHSU-CME.

February 9—**March of Dimes—Sharpening the Focus on Prenatal Care.** Portland. Sunday. Red Lion/Lloyd Center. Contact: OHSU-CME.

February 27-March 2—**Update in Rheumatology.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

July 14-16—**Plastic Surgery for the Primary Care Physician.** Sunriver. Monday-Wednesday. Contact: OHSU-CME.

July 17-19—**Dermatology for the Primary Care Physician.** Sunriver. Thursday-Saturday. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

January 9-11—**Third Annual Hip-Knee Bioskills Workshop** (Sponsor: University of Utah). Thursday-Saturday. Snowbird. 15 hrs. Contact: Aaron Hofman, MD (801) 581-8664.

January 12-17—**Diagnostic Imaging** (Sponsor: University of Utah). Sunday-Friday. Park City Yarrow Holiday Inn. 21 hrs. Contact: Marcia Bilbao, MD (801) 581-1293.

January 16-18—**Arthroscopic Surgery 1986** (Sponsor: University of Utah). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 21.5 hrs. Contact: Robert Metcalf, MD (801) 581-7602.

January 19-23—**Neuroradiology: Head and Neck** (Sponsor: University of Utah). Sunday-Thursday. Sun Valley, ID. Credit: to be announced. Contact: Anne Osborn, MD (801) 581-4624.

January 19-24—**Snowbird Symposium in Advanced Rheumatology** (Sponsor: University of Utah). Sunday-Friday. Snowbird. 20 hrs. Contact: John Ward, MD (801) 581-8664.

January 20-23—**International Biomedical Engineering Symposium** (Sponsor: University of Utah). Monday-Thursday. Salt Palace, Salt Lake City. 18 hrs. Contact: J. Andrade, PhD (801) 581-5908.

January 23-26—**Contemporary Approaches/Sexual Function/Dysfunction** (Sponsor: University of Utah). Thursday-Sunday. Park City Yarrow Holiday Inn. 20 hrs. Contact: Clare Turner (801) 581-5908.

February 1—**Eating Disorders** (Sponsor: University of Utah). Saturday. University Union Building, Salt Lake City. 6 hrs. Contact: Greta Bruinsma (801) 581-8989.

February 11-14—**14th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. 31 hrs. Contact: Linda Twitchell (801) 581-8633.

February 15-19—**27th Annual OB/Gyn Update** (Sponsor: University of Utah). Saturday-Wednesday. Park City Yarrow Holiday Inn. 15 hrs. Contact: James Scott, MD (801) 581-5501.

February 19-22—**Perinatology Update** (Sponsor: University of Utah). Wednesday-Saturday. Park City Yarrow Holiday Inn. 16.5 hrs. Contact: James Scott, MD (801) 581-5501.

February 22-March 1—**9th Annual Update in Clinical Microbiology/Immunology** (Sponsor: University of Utah). One week. Park City Yarrow Holiday Inn. 25 hrs. Contact: John Matsen, MD (801) 581-7480.

March 1—**Intermountain Association of Pathologists Annual Winter Meeting** (Sponsor: University of Utah). Saturday. Westin Hotel Utah, Salt Lake City. 4 hrs. Contact: Carl Kjeldsberg, MD (801) 581-3283.

March 2-8—**Advances in Internal Medicine** (Sponsor: University of Utah). Sunday-Saturday. Snowbird. 25 hrs. Contact: Jennifer Fossum (801) 581-3581.

March 3-7—**Surgical Pathology Workshops** (Sponsor: University of Utah). Monday-Friday. Park City Yarrow Holiday Inn. 20 hrs. Contact: Karen Rasmussen (801) 268-7150.

March 5-7—**Common Problems in Pediatrics** (Sponsor: University of Utah). Wednesday-Friday. Salt Lake City. 12 hrs. Contact: Wendy Ellis (801) 363-1887.

March 6-7—**2nd Annual Symposium in Organ Transplantation.** (Sponsor: University of Utah). Thursday-Friday. 14 hrs. Park City Yarrow Holiday Inn. Contact: Karen Engstrom, RN (801) 581-2634.

March 6-7—**Utah Ophthalmological Society Annual Park City Winter Meeting: Corneal Disease** (Sponsors: Utah Ophthalmological Society and University of Utah). Thursday-Friday. Holiday Inn/Yarrow, Park City. Contact: Pam Hanson, (801) 355-5290.

March 9-15—**Medical and Surgical Advances in G.I.** (Sponsor: University of Utah). Sunday-Saturday. Park City Yarrow Holiday Inn. 25 hrs. Contact: Jennifer Fossum (801) 581-3581.

March 11-21—**Perinatal Transport Workshop** (Sponsor: University of Utah). Tuesday-Friday. Little America Hotel, Salt Lake City. 60 hrs. Contact: Jeanne Ferretti; (801) 581-7085.

March 17-21—**6th Annual Nutrition in Contemporary Medicine Symposium** (Sponsor: University of Utah). Monday-Friday. Shadow Ridge Hotel, Park City. 30 hrs. Contact: Jennifer Fossum (801) 581-3581.

April (dates to be announced later)—**Orthopedics—Shriners Hospital Scientific Session** (Sponsor: University of Utah). Shriners Hospital, Salt Lake City. 7 hrs. Contact: Sherman Coleman, MD (801) 581-5307.

April 10-12—**Neurology for the Practitioner** (Sponsor: University of Utah). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 18 hrs. Contact: J. Richard Baringer, MD (801) 581-8664.

May 11-16—**Radiologic Subspecialty Updates.** (Sponsor: University of Utah). Sunday-Friday. Hong Kong. 24 hrs. Contact: David Bragg, MD (801) 581-8188.

June 22-26—**School on Alcoholism and Other Drug Dependencies** (Sponsor: University of Utah). Sunday-Thursday. University of Utah Health Science

Center, Salt Lake City. 26 hrs. Contact: James Swenson, MD (801) 581-7985.

July 13-18—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, MY. 23 hrs. Contact: John Matsen, MD (801) 581-7480.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

December 20—**Gunshot Trauma.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 3—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 10—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 16-17—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

January 17—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 21—**Osteoporosis:DX and RX.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

January 22 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

January 23 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

January 23-24—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

January 24—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center. 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

January 24 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

January 24-25—**Eye Care for Primary MDs.** Seattle. Friday-Saturday. Westin. Contact: U/W.

January 28—**Immunization Updates.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

January 31—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 31-February 1—**Updates in Cardiology.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

February 1-8 (IDAHO)—**Sports Medicine.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 6-7—**Neurology Update.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

February 7—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 7-8—**Clinical Problems in Urology.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact:VMMC.

February 8-15 (IDAHO)—**Musculoskeletal Radiology.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 14—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 15-22 (IDAHO)—**Endocrinology/Nutrition.** Sun Valley. One week. Elkhorn Resort. Contact: U/W.

February 18—**Antiviral Strategies.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

February 19 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Columbus Hospital. Contact: U/W.

February 20 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

February 20-22 (HAWAII)—**Ethical Problems for Surgeons.** Molokai. Thursday-Saturday. Sheraton Molokai. Contact: U/W.

February 21—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 21 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

February 23-March 1 (HAWAII)—**Surgical Emergencies.** Kona. Sunday-Saturday. Royal Waikoloa. Contact: U/W.

February 25—**Child Rearing Practices—1986.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

(Continued on Page 880)

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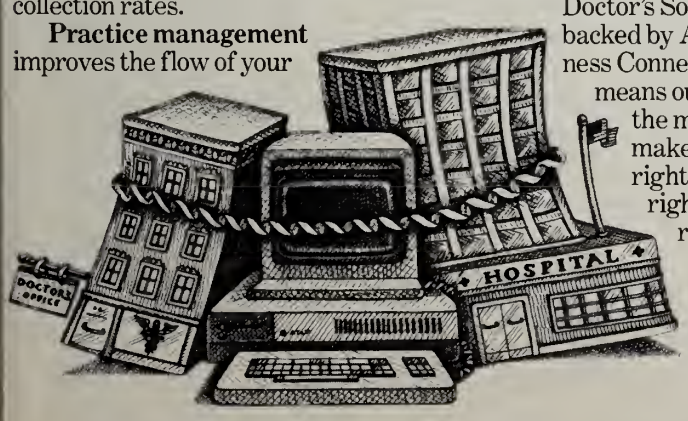

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(Continued from Page 878)

February 28—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 28-March 1—**Neurology—Past, Present, Future.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

March 7—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 14—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 15-22 (HAWAII)—**Medical Malpractice.** Maui. One week. Royal Lahaina. Contact: U/W.

March 18—**Shoulder Injuries.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 19 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

March 20 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

March 21 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

March 21—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 21-22—**Medicine for Psychotherapists.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

March 22-29 (HAWAII)—**Office Diagnosis and Therapy.** Kauai. One week. Kauai Sheraton. Contact: U/W.

March 22-29 (HAWAII)—**Ortho/OBGYN/Pain/Obesity/Surgery.** Kauai. One week. Kauai Sheraton. Contact: U/W.

March 25—**What's New In Imaging.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 28—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 29—**Radiology Northwest.** Seattle. Saturday. UW Health Sciences Building. Contact: U/W.

April 3-5—**Oncology.** Seattle. Thursday-Saturday. Westin Hotel. Contact: U/W.

April 4—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 5—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 5-12 (HAWAII)—**Drug Therapy.** Kauai. One week. Sheraton Princeville. Contact: U/W.

April 7-18—**Rehab Medicine Review.** Seattle. Monday-Friday. Seattle Sheraton. Contact: U/W.

April 11—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 15—**G.E. Reflux and Surgery.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 16 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Columbus Hospital. Contact: U/W.

April 17 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

April 18—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 18 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

April 22—**Common Knee Strains/Sprains.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

April 25—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 1-5—**Psychomotor Skill.** Seattle. Thursday-Monday. Westin Hotel. Contact: U/W.

May 2—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 2-3—**Functional Disease.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8-9—**MKSAP VII Review Course.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

May 9—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 16—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 20—**Hyperlipidemias.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 21 (MONTANA)—**Montana Medicine Lecture Series.** Great Falls. Wednesday. Deaconess Medical Center. Contact: U/W.

May 22 (MONTANA)—**Montana Medicine Lecture Series.** Billings. Thursday. Deaconess Hospital. Contact: U/W.

May 23 (MONTANA)—**Montana Medicine Lecture Series.** Missoula. Friday. St. Patricks Hospital. Contact: U/W.

May 23—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 27—**Hyperlipidemia.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

May 30—**Riverton Hospital Lecture Series.** Seattle. Friday. Riverton Hospital. Contact: U/W.

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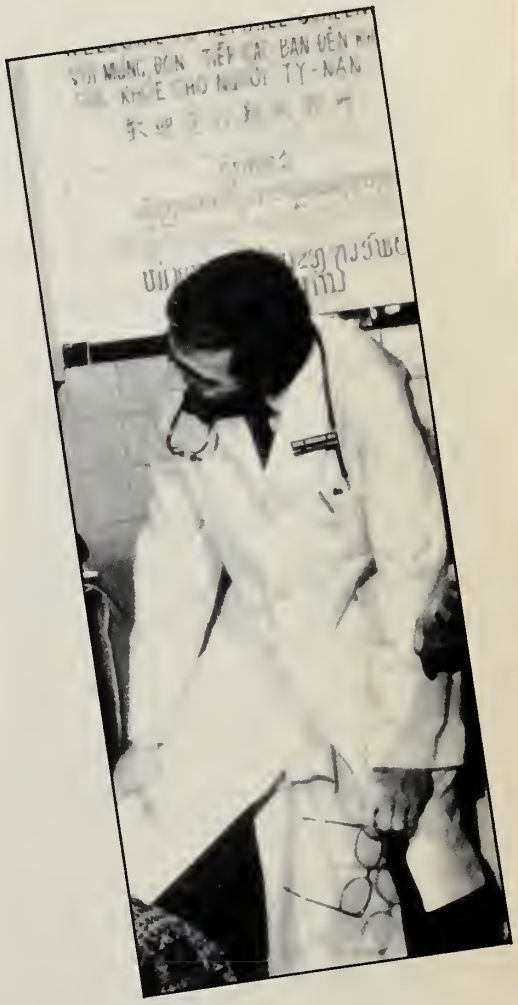

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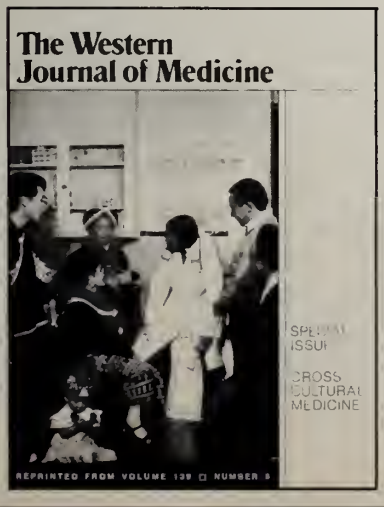

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THE UNIVERSITY OF UTAH, Department of Family and Community Medicine, is seeking two BC/BE Family Physicians for clinical positions in university-run community health centers. The population served is a challenging, multi-ethnic one. Full range of family practice including obstetrics, is required. Flexibility exists for resident teaching, research, and post-graduate work towards MSPH. Attractive base salary, benefits, practice incentive, and vacation time. If interested call or write Dr Stephen Ratcliffe, University of Utah, DFCM, 50 North Medical Dr., Salt Lake City, UT 84132; (801) 581-5529.

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FAMILY PRACTITIONER—Tulare County, California. Board certified/eligible Family Practitioner to practice in an outpatient clinic, which includes inpatient duties, with 13 physicians. Consider a semi-rural lifestyle with cultural amenities, the Coast and the Sierra Nevada Mountains easily accessed. Salary: $81,236 to $85,376 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. An Affirmative Action Employer.

OB/GYN—Tulare County, California. Board certified/eligible OB/GYN to practice in an outpatient clinic, which includes inpatient duties, with 13 physicians. Consider a semi-rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $88,837 to $93,365 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. An Affirmative Action Employer.

OPPORTUNITY AVAILABLE for Family Practice physician interested in surgery and OB in group practice in desirable rural area. Clinic and hospital well-equipped. Call/write F. L. Nutter, Administrator, 1101 Texas, Deer Lodge, MT 59722; 1 (406) 846-2212.

INTERNIST or internal medicine subspecialist to associate with recently established Internist/Rheumatologist in growing Northern California community of 150,000. Incentives offered. Reply with CV to Rex Adams, MD; PO Box 5375, Modesto, CA 95352-5375.

GENERAL INTERNAL MEDICINE SPECIALIST position open with 35 member multispecialty group. Excellent practice opportunity; full range of benefits; immediate shareholder status; all practice costs paid. For more information contact: Colin Wells, MD, Recruitment Coordinator, or David Graham, Associate Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401.

PHYSICIANS WANTED

FAMILY PRACTICE PHYSICIAN—Salaried position in rural health care system serving tri-cultural population (Hispanic, Navajo, and Anglo) in Northwest New Mexico; Spanish language very desirable. Salary level negotiable depending on qualifications; liberal fringe benefits package. Contact John Glass, Presbyterian Medical Services, PO Box 2267, Santa Fe, NM 87504; (505) 982-5565.

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ONCOLOGIST/HEMATOLOGIST needed to join two other Oncologists/Hematologists in a 32-member multispecialty group located in San Luis Obispo, California. Board certified or eligible. Excellent practice opportunity: benefits and retirement program; all practice costs paid; immediate shareholder status. Send CV to: San Luis Medical Clinic, Ltd., Attn: Colin J. Wells, MD, Recruitment Coordinator, 1235 Osos St., San Luis Obispo, CA 93401.

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FAMILY PHYSICIAN—Board certified or eligible to join the Family Practice Department of a busy, primary care based multispecialty group. Excellent opportunity for growth. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 E. Kincaid, Mt. Vernon, WA 98273; (206) 428-2524.

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(Continued on Page 884)

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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: June 5-7, 1986, Loews Ventana Canyon Resort, Tucson.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1986: date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1986: date and place to be announced.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1986: date and place to be announced.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1986: date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting and Scientific Session: May 8-11, 1986, John Ascuaga's Nugget, Sparks.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Interim Meeting: November 15-16, 1985, Holiday Inn de Las Cruces, Las Cruces. Centennial Meeting: April 30-May 2, 1986, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 25-27, 1986, Valley River Inn, Eugene.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1986: date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: 1986: date and place to be announced.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1986, Jackson Lake Lodge, Moran.

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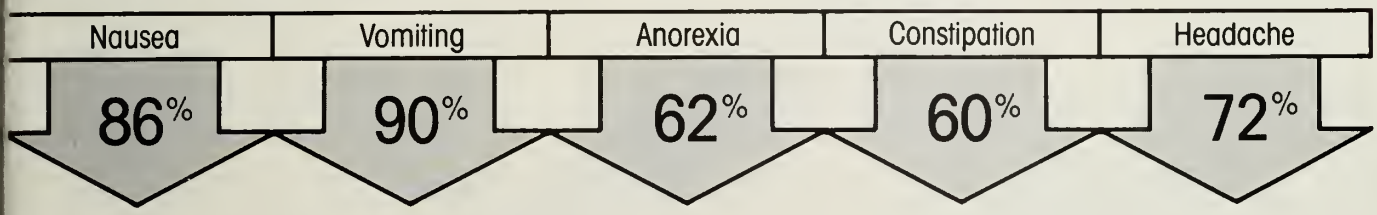

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More than three times as many amitriptyline patients as Limbitrol patients dropped out of therapy because of side effects, although the incidence of side effects was similar. Caution patients against the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to lowest effective amount in elderly patients.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ **2.** Feighner JP, *et al: Psychopharmacology 61*:217-225, Mar 22, 1979.

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Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

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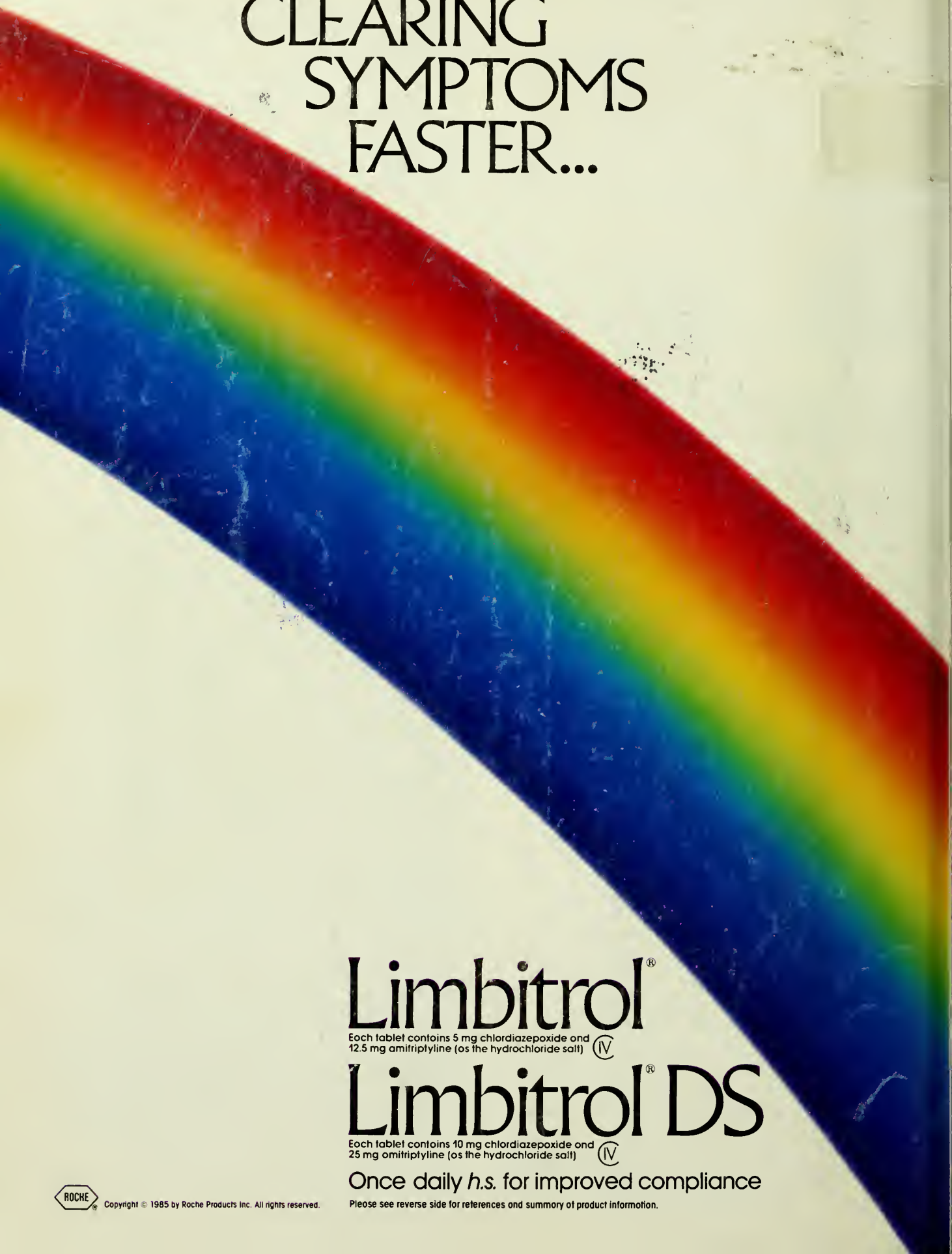

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